

American Journal
of
Digestive Diseases
Volume 14

The American Journal of DIGESTIVE DISEASES

An Independent Publication

DEVOTED TO GASTRO-ENTEROLOGY AND NUTRITION

ORIGINAL CONTRIBUTIONS

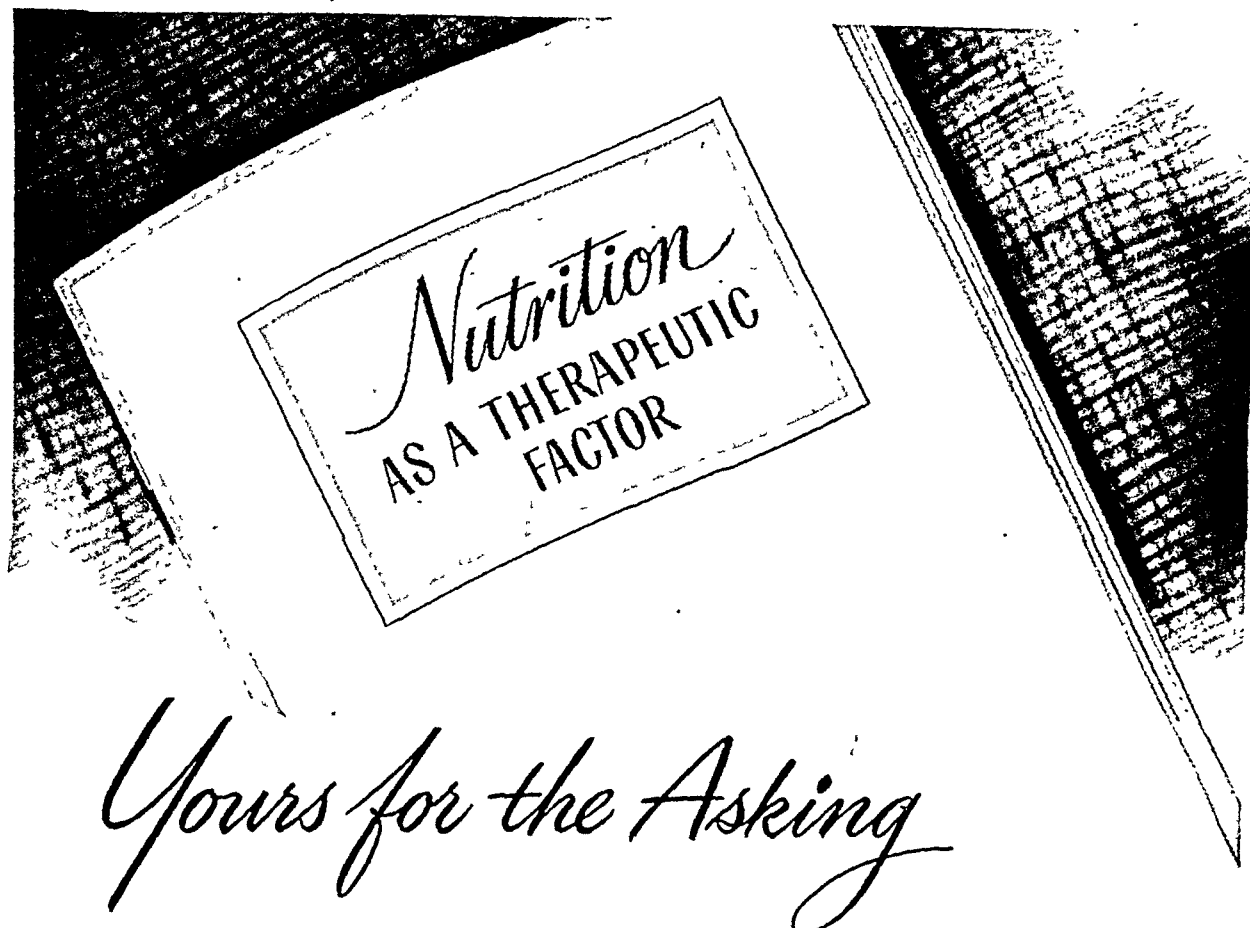
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January, 1947

Number 1

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THIS INFORMATIVE COMPENDIUM
ON A TIMELY SUBJECT

PHYSICIANS are invited to use the appended coupon to request a complimentary copy of the new brochure "Nutrition As A Therapeutic Factor." In a terse, straightforward manner, this compendium of current thought presents the remarkable strides made during the last decade in the use of nutritional factors as therapeutic weapons. The presentation

concisely outlines present aspects of nutritional therapy providing information and data valuable in everyday practice. The applicability of the various nutrients—including salt and water—in the treatment of many disease entities is presented, adding to the practical utility of the brochure. The Wander Company, 360 N. Michigan Ave., Chicago 1, Illinois.

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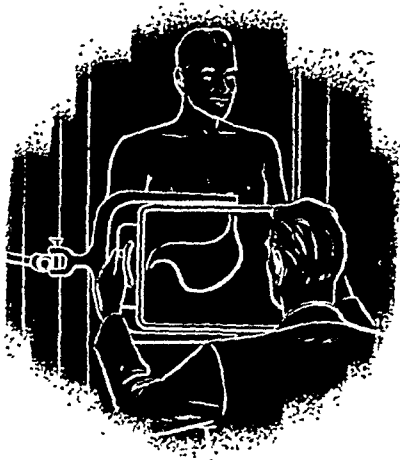
Volume 14

February, 1947

Number 2

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Among the Basic Points of Dietary Adjustment



A good nutritional status is especially important in the gastrointestinal patient, regardless of the nature or location of the lesion. Healing or prevention of future breakdowns is possible only when the organism is fully capable of mobilizing its local cellular defense mechanisms, a situation not compatible with a poor nutritional state.

A good breakfast is universally acknowledged as being essential in any sound nutritional program.

A widely accepted basic breakfast pattern—fruit, cereal, milk, bread and butter—aids in attaining this objective. The cereal serving, consisting of cereal (ready to eat or hot), milk and sugar, is an important component of this breakfast; it provides virtually all essential nutrients except ascorbic acid, and meets the requirements for chemical and mechanical blandness so frequently demanded in gastrointestinal diets. The quantitative contribution made by the serving of 1 ounce of hot or ready-to-eat cereal* (whole grain, enriched, or restored to whole grain values of thiamine, niacin, and iron), 4 ounces of milk, and 1 teaspoonful of sugar, is indicated in the table.

CALORIES.....	202	PHOSPHORUS....	206 mg.
PROTEIN.....	7.1 Gm.	IRON.....	1.6 mg.
FAT.....	5.0 Gm.	VITAMIN A.....	193 I.U.
CARBOHYDRATE..	33.0 Gm.	THIAMINE.....	0.17 mg.
CALCIUM.....	156 mg.	RIBOFLAVIN.....	0.24 mg.
NIACIN.....	1.4 mg.		

*Composite average of all breakfast cereals on dry weight basis.

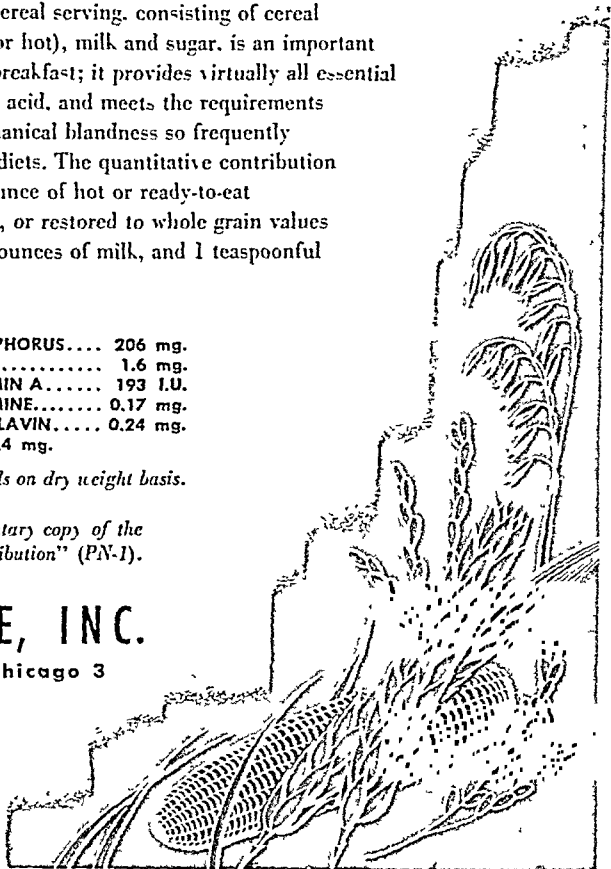
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March, 1947

Number 3

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... in B-Vitamin Therapy

Deficiencies of B vitamins are more often multiple than single. For rapid nutritional rehabilitation, therapy should therefore be based on replacement with the complete natural B-Complex, strengthened with massive doses of the individual factors proven nutritionally indispensable in man.^{1,2}

• Such authoritative opinions are cogent reasons for prescribing Allbee Robins capsules. They incorporate dried primary yeast—the richest source of B-Complex vitamins—fortified with potent amounts of four crystalline fractions—a formula that has proven brilliantly effective in practice.

FORMULA: Each capsule contains:

Thiamine	15 mg.
Riboflavin	10 mg.
Niacinamide	50 mg.
Calcium Pantothenate ..	10 mg.
Dried Primary Yeast	292 mg.

plus these and other factors as found in dried primary yeast.

1. Jolliffe, N.; J.A.M.A. 129:613, 1945

2. Spies, T.; J.A.M.A. 125:245, 1944

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Volume 14

April, 1947

Number 4

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Ulcer Management...

Multiple Feedings... and Cereals



IN THE active management of the acute ulcer flare-up, multiple small feedings are a sine qua non in the therapeutic regimen. Bland nutritious feedings of properly chosen foods aid in continuous acid neutralization and go far in preventing recurrence of the typical epigastric distress and pain.

The cereal serving, consisting of breakfast cereal (ready to eat or hot), milk, and sugar, is of universally recognized value in the dietary of peptic ulcer. Except for those purposely made different through the inclusion of bran, cereals are bland, mechanically as well as chemically. When served with cream instead of milk, the cereal serving presents even greater acid inhibitory properties. The large variety of cereals available goes far in preventing monotony in the ulcer diet, since a different type of cereal can be eaten daily without too frequent repetition.

The nutritional contribution made by the serving of 1 ounce of hot or ready-to-eat cereal* (whole grain, enriched, or restored to whole grain values of thiamine, niacin, and iron), 4 ounces of milk, and 1 teaspoonful of sugar, is indicated in the table.

CALORIES.....	202	PHOSPHORUS....	206 mg.
PROTEIN.....	7.1 Gm.	IRON.....	1.6 mg.
FAT.....	5.0 Gm.	VITAMIN A.....	193 I.U.
CARBOHYDRATE.	33.0 Gm.	THIAMINE.....	0.17 mg.
CALCIUM.....	156 mg.	RIBOFLAVIN....	0.24 mg.
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**Composite average of all breakfast cereals on dry weight basis.*

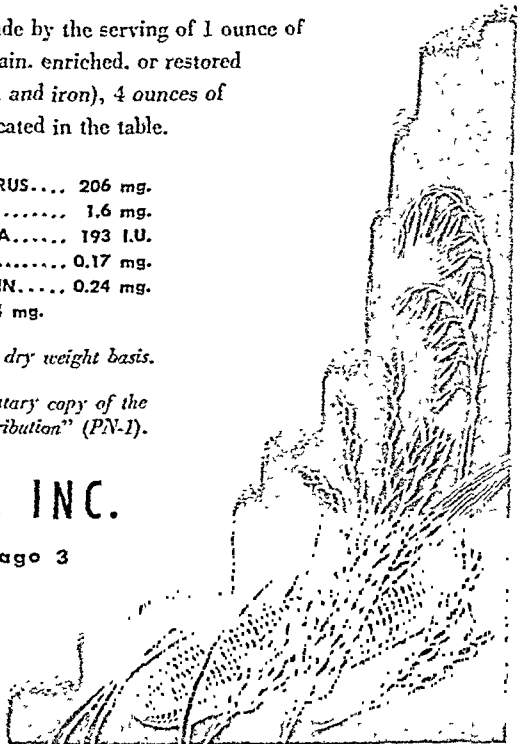
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Volume 14

May, 1947

Number 5

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*"as soon as injury
or disease occurs..."*

"... malnutrition almost always begins."¹

Nutritive replacement must be equally prompt.

According to a recent editorial in the J.A.M.A.,
"Vitamin deficiencies commonly encountered
in clinical practice are multiple ...

Treatment for a deficiency involves
administration ... of large enough doses
of the vitamin to be of therapeutic value and
continuation of this treatment for long
enough periods to assure a satisfactory
therapeutic trial."²

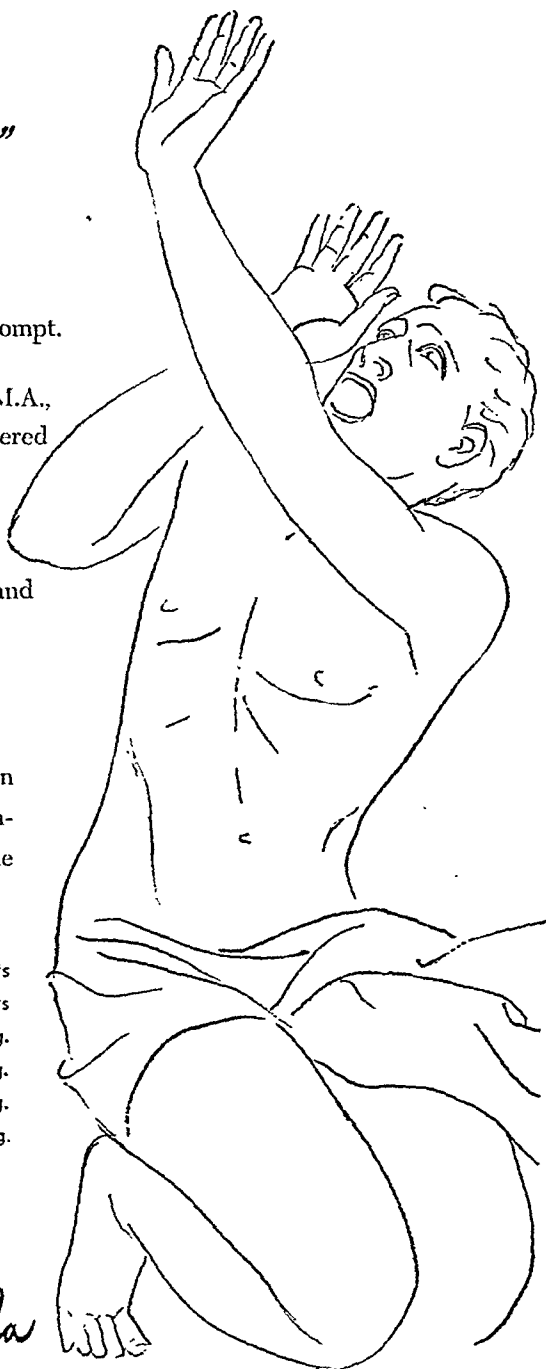
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Capsules contain *truly therapeutic* poten-
cies of *all the essential vitamins*. A single
capsule contains:

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Vitamin D.....	1,000 units
Thiamine HCl	5 mg.
Riboflavin	5 mg.
Niacinamide.....	150 mg.
Ascorbic Acid	150 mg.

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1. Peters, J. P., and Elman, R.: J.A.M.A. 124:1206 (Apr. 22) 1944.
2. Council on Foods and Nutrition: J.A.M.A. 131:666 (June 22) 1946.

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When Active Therapy is concluded



AFTER the therapeutic situation at hand has been concluded, consideration must be given to the future health of the patient.

A well-formulated plan of living must be outlined, not least important in which is the nutrition plan to be followed.

Sound dietary planning calls for a good breakfast, one which provides from one-fourth to one-third of the daily caloric and nutrient needs. A basic breakfast pattern, widely accepted as nutritionally sound, provides fruit, cereal (hot or ready to eat), milk, bread and butter.

The serving of breakfast cereal, milk, and sugar is an important component of this breakfast. It provides a wide variety of essential nutrients, including sufficient quantities of the B-complex vitamins for utilization of the caloric food energy provided. The quantitative contribution made by the serving of 1 ounce of ready-to-eat or hot cereal* (whole grain, enriched, or restored to whole grain values of thiamine, niacin, and iron), 4 ounces of milk, and 1 teaspoonful of sugar, is indicated by the table.

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CALCIUM.....	156 mg.	RIBOFLAVIN....	0.24 mg.
NIACIN.....	1.4 mg.		

**Composite average of all breakfast cereals on dry weight basis.*

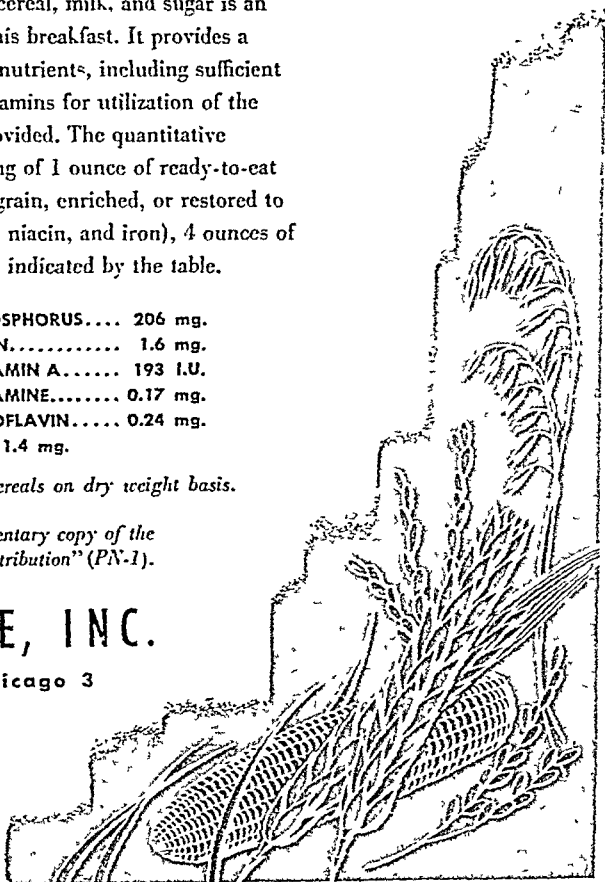
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July, 1947

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PERIPHERAL EDEMA

due to blood vessel permeability

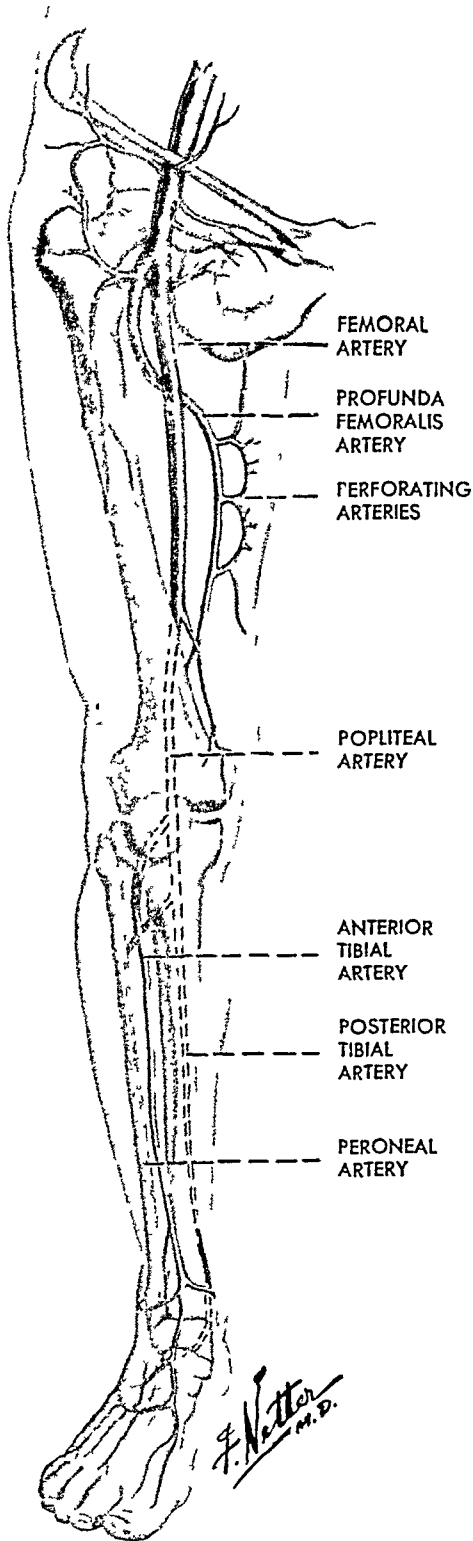
Peripheral edema is observed quite commonly without any cardiac or renal disease. In many such cases a disturbance of vascular permeability is the basic cause. In some the edema is transitory and recurrent as in angioneurotic edema. In others it is fairly constant.

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Supplied in 2 grain capsules—bottles of 100



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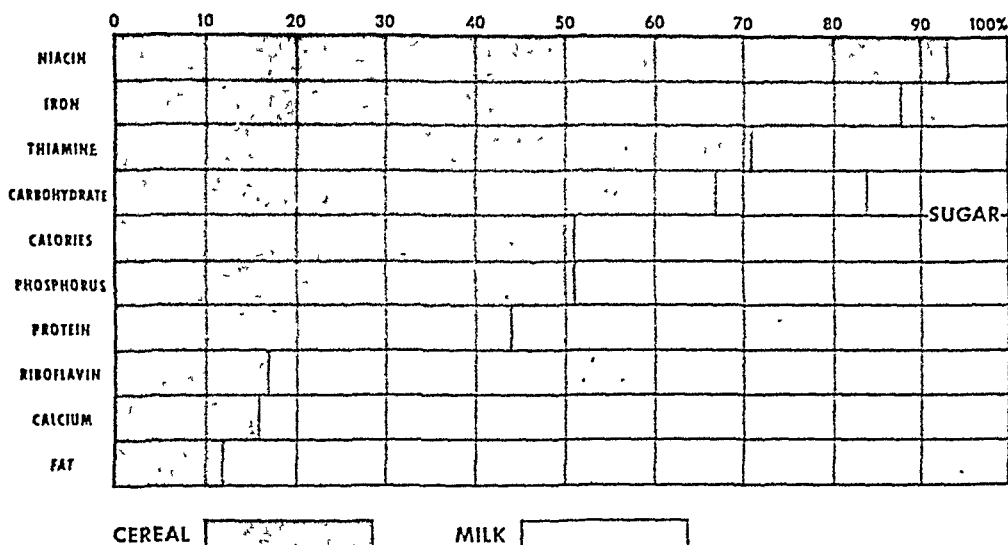
Volume 14

August, 1947

Number 8

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Excellent Nutritional Supplementation



The chart reproduced above illustrates the excellent manner in which the foods comprising the cereal serving (breakfast cereal, milk, and sugar) complement each other from a nutritional standpoint. It depicts the percentage of important nutrients contributed by each food. Note that each of the two major components of the cereal serving contributes most of those nutrients supplied less generously by the other. Hence the cereal serving is a balanced combination of foods, an example of the importance of selecting foods wisely for the completeness of their combined contributions. Furthermore, the amounts of B-complex vitamins contained in the cereal serving are more than adequate to permit metabolic utilization of the carbohydrates provided. The quantitative composition of 1 ounce of cereal* (whole grain, enriched, or restored to whole grain values of thiamine, niacin, and iron), 4 ounces of milk, and 1 teaspoonful of sugar is shown in the table.

CALORIES.....	202	PHOSPHORUS....	206 mg.
PROTEIN.....	7.1 Gm.	IRON.....	1.6 mg.
FAT.....	5.0 Gm.	THIAMINE.....	0.17 mg.
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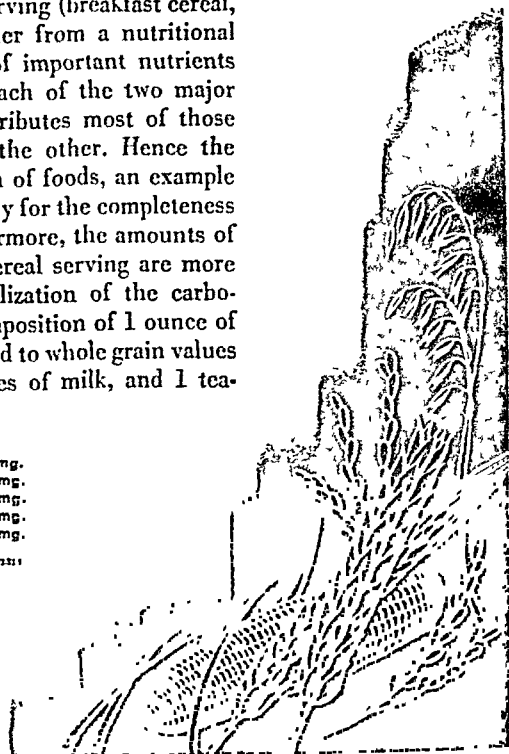
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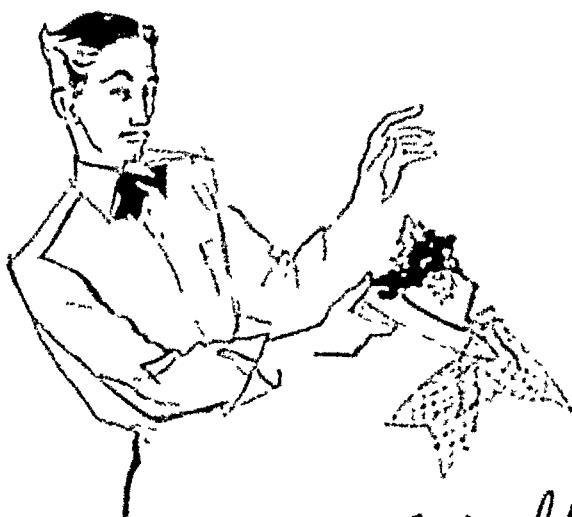
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IN the management of acute enteritis, the essential features of the prescribed diet are blandness and ease of digestion. Usually self-limited, these acute disturbances often do not require a starvation regimen which in many instances may prove detrimental.

Breakfast cereals—ready to eat or hot—fit well into the dietary of acute enteritis. They present excellent nutrient values together with physical and chemical blandness. Easily digested without imposing a burden on the patient's digestive capacity, cereals (except those made purposely different by the inclusion of bran) leave virtually no residue which might lead to peristaltic stimulation or undesirable decomposition.

The excellent nutritional contribution made by the cereal serving composed of 1 ounce of hot or ready-to-eat cereal* (whole grain, enriched, or restored to whole grain values of thiamine, niacin and iron), 4 ounces of milk and 1 teaspoonful of sugar is indicated by the table.

CALORIES.....	202	PHOSPHORUS....	206 mg.
PROTEIN.....	7.1 Gm.	IRON.....	16 mg.
FAT.....	5.0 Gm.	THIAMINE.....	0.17 mg.
CARBOHYDRATE..	33.0 Gm.	RIBOFLAVIN....	0.24 mg.
CALCIUM.....	156 mg.	NIACIN.....	1.4 mg.

*Composite average of all breakfast cereals on dry weight basis.

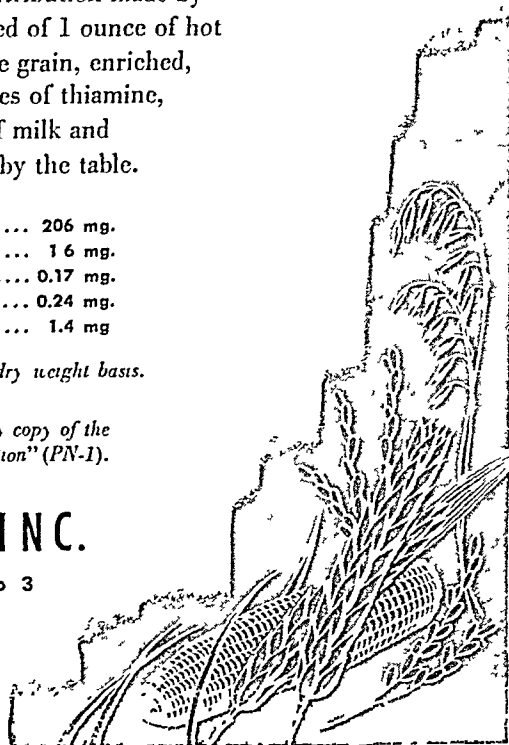
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Breakfast... and the Daily Nutrient Distribution



THE significance of breakfast as an important means of meeting the daily dietary allowances as suggested by the National Research Council was vividly demonstrated in a recent study.†

This investigation revealed that subjects who skipped breakfast entirely or who ate a skimpy breakfast failed to receive their daily nutritional requirements in the other two meals of the day. In the light of these findings, breakfast assumes new importance for the patient afflicted with gastrointestinal disease in whom overburdening of the G. I. tract should be avoided.

Virtually all nutritionists agree that breakfast should supply from one-fourth to one-third of the daily caloric and nutrient needs. A widely endorsed breakfast pattern, composed of fruit, cereal, milk, bread and butter, aids in organizing a well-rounded morning meal. The cereal serving—consisting of hot or ready-to-eat breakfast cereal, milk and sugar—is a universally recommended component of this breakfast. This serving contributes worth-while amounts of many essential nutrients, including biologically complete proteins, B-complex vitamins, and important minerals.

The quantitative contribution made by 1 ounce of ready-to-eat or hot cereal* (whole grain, enriched, or restored to whole grain values of thiamine, niacin and iron), 4 ounces of milk, and 1 teaspoonful of sugar is indicated by this table.

CALORIES.....	202	PHOSPHORUS....	206 mg.
PROTEIN.....	7.1 Gm.	IRON.....	1.6 mg.
FAT.....	5.0 Gm.	THIAMINE.....	0.17 mg.
CARBOHYDRATE..	33.0 Gm.	RIBOFLAVIN.....	0.24 mg.
CALCIUM.....	156 mg.	NIACIN.....	1.4 mg.

*Composite average of all breakfast cereals on dry weight basis.

† Jackson, P., and Schuck, C.: *Dietary Habits of Public University Women*, *J. Home Econ.* 39:334 (June) 1947.

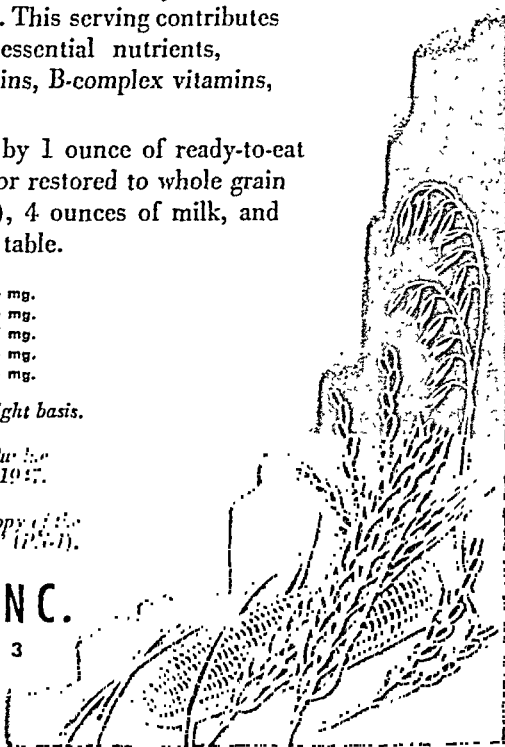
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Chronic Peptic Ulcer In Ninety-Four Diabetics

By

M. N. WOOD, M. D.*
BOSTON, MASS.

THE MATERIAL in this report has been prepared to show the clinical features, course, and therapeutic management of peptic ulcer as it occurred in ninety-four diabetic individuals.

Diabetic dietary treatment is not easy when the additional burden of a peptic ulcer is present. The ensuing data indicates that such a condition can be a serious one; for many of the patients subsequently developed serious complications from either the ulcer or the diabetes.

Fifty-nine patients, who hereafter will be referred to as Group I, had diabetes for varying periods of time before the onset of ulcer symptoms. The remaining thirty-five, who will be referred to as Group II, had ulcer first, and developed true diabetes later. In both groups, but mostly in Group I, instances were seen where the failure to interpret the symptoms led to delay in the diagnosis, and possibly to complications. In Group II failure of some patients to appreciate the seriousness of the diabetic state resulted in coma which could have been prevented. In general this grouping has shown that the habits formed from a long association with one disease has had an effect upon the eventual course of the other.

Few cases of this nature have been reported in the American literature. Jankelson and Rudy¹ reported thirteen cases of glycosuria and peptic ulcer; Rothenberg and Teacher², nine. Both reports were characterized by a high percentage of complicated cases with unusual clinical features. In the first report the diagnosis of a true diabetic state was doubtful in six individuals. The authors considered the glycosuria to be due to a chronic pancreatitis probably secondary to a posterior wall ulcer that had penetrated into that organ. In these cases the mild glycosuria cleared following adequate ulcer management. This series includes only those cases in which the diagnosis of diabetes and peptic ulcer was definitely established. Borderline diabetics have been excluded, and so have those with suspicious abdominal symptoms, but no x-ray evidence to support the clinical impression.

During the years 1934 through 1944 twelve thousand diabetics have been observed at the George F. Baker Clinic. Peptic ulcer was found to be present in 0.78%. The disease occurred in 68 males and 26 females whose age ranged from 23 to 74 years at the beginning of symptoms. In the main, however, the ulcer had its onset in the older age group. Seventy-three were past the age of forty when symptoms first developed.

Symptoms were caused by single duodenal ulcers in 74 cases, by single gastric in 11. X-ray showed the

presence of combined gastric and duodenal ulcers in three instances. Surgical specimens revealed five additional coexistent gastric and duodenal lesions. The incidence for combined ulcers is 8.5%.

SYMPTOMS

Typical ulcer pain in respect to severity, time relationship, and point localization was definitely lacking in 50 patients. Four, in fact, reported no pain whatsoever. Vague generalized abdominal discomfort with no relationship to meals was the main complaint; something which the patient usually described as "mild indigestion, didn't really bother me much." Forty-four described definite pain symptoms fairly well localized, and having an association with an empty stomach. In only nine, however, was the pain severe enough to wake the patient up at night.

Nausea was present in 52, emesis in 42. It must be said that owing to the vagueness of the initial symptoms in many cases, the date of onset of the ulcer may have been erroneous. Complications, particularly retention, have developed in some patients soon after the onset of the ulcer as it was determined here. In such cases where nausea and vomiting seemingly was a prominent symptom at the outset, it was difficult to determine from the vague histories just when the symptoms were referable to an uncomplicated ulcer, or to one beginning to cause trouble. Twelve cases in the series could be considered in this light.

Studying the symptoms separately from each group, it was found that the people in Group I had the largest proportion of ill-defined abdominal complaints. 59.3% of this group had ulcer symptoms which were vague and confusing contrasted to Group II where 42.9% were determined vague.

Nausea occurred in 61.0% of Group I, but in Group II it was present in only 45.7%. Vomiting was more frequent, too, in the first group — 47.4% as compared to Group II with 40.0%.

ACIDITY

Data from complete gastric analysis was obtained in 58 cases. In the fasting samples, only seven patients had free hydrochloric acid values above 41 degrees (11.8%). The highest reading was 70 degrees. Among 39 patients with fasting values ranging from 0-20 degrees, 21 had no free hydrochloric acid (F.HCL) at all in the first specimen. Readings 21-40 degrees were obtained in twelve.

At the peak of the rise following stimulus, acid values were still below 41 degrees in 26 cases, above in 32. Five had absence of F.HCL even after histamine. Readings below 10 were seen in four, from 10-20 in six, from 21-40 in eleven. In sixteen, F.HCL ranged

*From The George F. Baker Clinic. New England Deaconess Hospital, Boston, Mass.
Submitted July 5, 1946.

between 41 and 60; between 61 and 80 in ten, and between 81 and 120 degrees in six.

Group I was again found to have the greatest percent of unusual features. Only one had hyperacidity. Three out of five with absent F.HCL were from this group. 59.4% retained values below 41 degrees even after histamine, and 84.4% did not rise above 60 degrees.

In Group II the F.HCL response to stimulus was much better. Only 26.9% remained below 41 degrees compared to 59.4% in Group I. 42.3% reached values above 61 degrees contrasted to the 15.6% in the first group. Table VI gives the complete data.

COMPLICATIONS

During the course of their disease, 62 people had complications develop in the ulcer. Twelve patients were afflicted with two or more major types of complications at different stages in the ulcer history. Five had hemorrhage and perforation, three hemorrhage and obstruction, three obstruction and perforation, and one had obstruction, hemorrhage, and perforation with subsequent common duct duodenal fistula. Single complications existed in fifty individuals. Eight, who had some bleeding from the ulcer as determined by occult blood in the stool and low red blood counts, have been included with the total cases complicated, but were not considered as serious cases. Excluding them, fifty-four individuals were found who presented the more serious type complications such as gross or massive hemorrhage, obstruction, perforation, or carcinoma developing in chronic gastric ulcer.

Five people died in the entire series; two from acute massive hemorrhage and one with generalized peritonitis from an acute perforation. Two were post-operative deaths: pulmonary embolism was the cause in one case. A laparotomy had been performed for undiagnosed abdominal complaints in a middle-aged female diabetic of eighteen years' duration. Previous G. I. x-rays had been negative, the gastric analysis was not helpful. Nevertheless, a duodenal ulcer was found, and it was the only thing discovered which could account for her symptoms. Post-operative obstruction and peritonitis following gastric surgery caused the other surgical death.

In all, thirteen major operations were performed for complications in this series. All of them will be referred to again when the respective complication group to which they belong is discussed.

RESPONSE TO TREATMENT

At the time last seen, forty patients were determined to have had complete relief from symptoms as a result of either medical or surgical treatment. Twenty were better off, but could not be considered free from symptoms. A definite recurrence in the form of hemorrhage, obstruction, perforation or symptoms occurred in thirty-four. Some who developed the initial symptoms of ulcer in the latter two or three years of this study have not been observed long enough to give a true indication of the actual recurrence rate in this group.

DIABETIC STATE

In the main the diabetic state was not changed with the onset of ulcer and its treatment. A few cases required more insulin, but in most instances the dose necessary for adequate control remained stable.

For simplicity sake, the diabetes has been classified according to the insulin requirement. Actually this does not indicate the true severity of the disease, but for the purpose here it is sufficient. Individuals requiring 0-25 units were called mild; from 26-50 units, moderate; from 51-75 units, moderately severe; and over 75 units, severe.

In Group I, before the onset of the ulcer, forty could be classified mild, eighteen moderate, and one moderately severe. Following ulcer treatment, a few people in the mild or moderate group who were near the upper borderline limit, or the lower limit respectively, slipped into the next group. However, the insulin dose did not change enough to make much actual difference, and in the final analysis thirty-five cases were still mild after treatment, and twenty were still moderate. Two mild cases and one moderate case became moderately severe. Coma subsequently developed in one previously mild case that had become moderately severe, and in one other moderate case whose insulin requirement had not changed.

In Group II, eighteen cases were mild, twelve moderate, and five moderately severe. Diabetic coma subsequently developed in five people from this group. Four out of five of the moderately severe cases had coma, one of them three times. The fifth coma was in a moderate case. It was interesting to note that ulcer distress had been characteristic, and pain a prominent symptom in all of them.

ARTERIOSCLEROSIS

Arteriosclerosis was a prominent feature in this series. The presence of arteriosclerosis (A. S.) was determined by the function of the heart and coronary arteries, by evidence of nephrosclerosis, the condition of the retinal or radial arteries, and by cerebral manifestations. By these methods the diagnosis of generalized A. S. was made in forty-two patients. Thirty-eight had A. S. in grades 1-4 as determined by palpation of the radial artery. Fourteen had no gross or other evidence of the condition.

Generalized arteriosclerosis was most frequent in Group I. 76.2% of the people with this diagnosis were from that group.

HEMORRHAGE

A newly acquired ulcer in an individual of middle, or past middle life is generally considered to have a more serious prognosis, especially when arteriosclerosis and hypertension as associated diseases are present to contribute to the severity of a complication such as hemorrhage. Emery and Monroe² state that: "A recently acquired ulcer in a fifty-year-old individual is more apt to bleed than a long standing one." Also: "A recently acquired ulcer in a fifty-year individual is more apt to bleed than a recent one in a younger person." The presence of arteriosclerosis and high blood

pressure have long been recognized as important factors in the prognosis of a bleeding-peptic ulcer. Thorsted⁴ states: "The incidence and mortality rate increases with age, and the presence of arteriosclerosis and hypertension."

On a large diabetic service one deals commonly with arteriosclerotic patients. The middle aged or older diabetic individual, especially the long duration one, is more prone to be afflicted with these extra hazards than the non-diabetic. Consequently one would expect bleeding to be a more serious problem in the average diabetic with peptic ulcer than in others.

In the entire series of ninety-four cases, we discovered twenty-four where gross, or acute massive hemorrhage was a complicating factor. Eight who had persistently strong positive tests for occult blood in the stool, and whose blood counts were low enough to indicate that some bleeding had taken place (Table I), have been included as bleeding ulcers, making a total of thirty-two cases, and an incidence of 34.0%. Occult blood was seen in fourteen other cases where the blood picture indicated that not much bleeding, if any at all, had taken place. None of these have been classified as bleeding ulcers in this report.

Bleeding occurred in twenty-four duodenal ulcers, five gastric, and in three cases with combined gastric and duodenal lesions where the exact source was not known. Five out of nineteen gastric ulcers bled giving an incidence of 26.3%.

Gross or acute massive hemorrhage was seen in 25.53% of the ulcers in this series, and in 75.0% of those that bled. We had fourteen cases of a first or single hemorrhage, five with a history of two, and five who had bled five or more times. Six cases were admitted with acute massive hemorrhage (Table II). Histories of one or more severe hemorrhages requiring transfusions were given in five additional cases. Two deaths resulted from massive bleeding. It was the first hemorrhage in one, the second in the other. Their ages were 57 and 78 respectively.

Black stools and blood counts indicated moderate hemorrhage on admission in seven cases (Table III). A history of melena, bloody vomitus or black stool was obtained in six other people.

ASSOCIATION OF ARTERIOSCLEROSIS AND HYPERTENSION

Tables IV-a and IV-b show that the diagnosis of generalized arteriosclerosis was made thirteen times in the gross and massive hemorrhage group of twenty-four cases. Hypertension was present in thirteen also. Generalized arteriosclerosis was found to be present in nine of the ten persons who had bled more than once, hypertension in eight. High blood pressure is not so prominent in those with occult blood only.

It seems that these people have suffered more than the average ulcer group. We have a large number of multiple bleeders, and two-time hemorrhages. In addition, we can expect some of them to have another recurrence. Jordan and Kiefer⁵ have pointed out a high recurrence rate in gross hemorrhage cases, especially those in which bleeding had occurred two or more

times. In forty-two cases of gross hemorrhage they found 43.0% had recurred in five years. With a history of two or more, 79.0% had recurred in a five-year period. They state: "In nearly all of these cases recurrence was in the form of another hemorrhage."

TABLE I. OCCULT BLOOD ONLY

Occult blood stool	R.B.C. Millions	Hemoglobin
3 plus -----	479	83%
3 plus -----	486	80%
3 plus -----	381	77%
4 plus -----	443	77%
3 plus -----	474	85%
4 plus -----	422	89%
3 plus -----	442	77%
3 plus -----	425	-----

TABLE II. ACUTE MASSIVE HEMORRHAGE

Hemorrhage where massive bleeding occurred	R.B.C. Millions	Hemoglobin
2nd -----	163	37%
1st -----	160	30%
1st -----	207	50%
1st -----	215 (died)	44%
2nd -----	190 (died)	36%
1st -----	212	31%

TABLE III. GROSS HEMORRHAGES

Hemorrhage where gross bleeding occurred	R. B. C.	Hemoglobin	stool
2nd -----	384	-----	black
2nd -----	330	70%	black
? (multiple bleeder) --	312	75%	black
1st -----	311	60%	black
1st -----	-----	73%	black
2nd -----	360	75%	black
1st -----	-----	69%	black

Many people believe that 50.0% of all ulcers which bleed in a person past forty-five years of age have had acute massive hemorrhage. Twenty-six in this group were past that age when bleeding first occurred. Our eleven cases give an incidence of 42.3%.

The overall incidence for bleeding seemed to be rather high so one naturally wonders whether the presence of diabetes had anything to do with this. When the patients were studied in groups one main difference in the course of the ulcer was seen which indicates that some factor in diabetes, or its treatment, has played a part in some of these cases. The separation also revealed a marked difference in the prognosis between the two groups.

According to groups, the hemorrhage cases will have the designation Group I(H) or Group II(H).

GROUP I(H)

In Group I 32.1% had bleeding from their ulcers. The average age at the onset of the ulcer was 53.0 years, and 55.8 years at the time the first bleeding episode occurred. Nine cases bled during the first year of the ulcer, five in the second, one in the third, and four after the third year.

Gross or acute massive hemorrhage was a feature in 63.6% of the bleeding cases in Group I(H). The thirteen people with this complication had an average age at the onset of the ulcer of 58.7 years, and at the time of the first hemorrhage their average age was 61.5 years. Thus the average duration of the ulcer was

2.8 years. Six bled initially during the first ulcer year, two in the second, one in the third, and the others in the fifth, sixth, eighth and tenth year. Acute massive hemorrhage, with two deaths, occurred in seven of the thirteen cases (53.8%). It occurred during the second hemorrhage in two people, during the first in three, and in two multiple bleeders where the exact hemorrhage could not be determined. Generalized arteriosclerosis appeared in eight cases, hypertension in nine.

In Group II (H) the total incidence for bleeding was 37.1%. The average age at the onset of ulcer symptoms was forty-five years. The first bleeding occurred at the average age of 53.4 years. Here the average duration of the ulcer was 8.4 years. Three cases bled in the first year, one in the second, but in the rest bleeding occurred first from four to fifteen years after the onset of the ulcer. With three exceptions these people bled first after the onset of diabetes. Two of

the least likely to bleed, and had been present an average of six years before gross bleeding occurred.

We also found a higher incidence in this younger group with old ulcers as compared to the older people in Group I (H) with new ulcers who theoretically are more prone to get into trouble. However, it was seen that the most serious bleeding cases were in the first group in spite of the lower over all bleeding incidence.

It may be that this difference is due to chance, but there is one factor to be considered: we have seen with two exceptions in Group II (H) (Table IV-b) that the serious bleeding occurred after the onset of diabetes. We do not think diabetes per se has caused this, but perhaps the effects of a diabetic diet on an unsuspected ulcer could, making a serious mechanical irritant which combined with the low tissue vitality subsequent to arteriosclerosis, helped to reactivate or produce a serious bleeding ulcer; one that may not have bled otherwise. We have the feeling that some of the bleeding in this

TABLE IV-a, GROUP I (H)

First hemorrhage in ulcer history, gross or massive	Second hemorrhage in ulcer history	Total No. of hemorrhages	Arteriosclerosis	Blood pressure	Duration D. M. at onset of ulcer
1st year	3rd year	2	Gen. A. S.	210/110	9 years
1st year	2nd year	2	Gen. A. S.	136/70	10 years
10th year	0	1	Grade 3	100/80	13 years
6th year	0	1	Grade 1	145/90	9 years
1st year	1st year	MX	Gen. A. S.	162/95	3 years
1st year	0	1	Grade 1	120/60	2 years
1st year	0	1	Grade 2	130/100	10 years
2nd year	0	1	Gen. A. S.	145/90	12 years
5th year	0	1	Gen. A. S.	180/80	23 years
3rd year	0	1	Gen. A. S.	146/60	10 years
8th year	8th year	2	Gen. A. S.	150/76	9 years
1st year	1st year	MX	Grade 3	150/80	4 years
2nd year	0	1	Gen. A. S.	230/120	13 years
Occult blood only					
1st year	0	1	None	110/70	5 years
2nd year	0	1	None	110/70	10 years
2nd year	0	1	Grade 3	140/90	4 years
1st year	0	1	Grade 2	130/80	18 years
2nd year	0	1	Grade 3	120/75	10 years
1st year	0	1	Gen. A. S.	120/70	19 years

these exceptions bled typically in the first year of their ulcer. One became a troublesome multiple bleeder both before and after the onset of diabetes; the other has never had a recurrence. The third man had tarry stool first during the fifth ulcer year, became inactive until the eighth year when he developed diabetes and a year later had four hemorrhages requiring transfusions.

Gross or massive hemorrhage was present in eleven of the thirteen cases in Group II (H) — 84.6% of the bleeding cases in their group. Acute massive hemorrhage occurred in four. The average age at first hemorrhage was 53.2 years, and at the onset of the ulcer was 47.2 years, giving the ulcer an average duration of six years (Table IV-b).

When we compare the gross and massive hemorrhage cases in the two groups, we find in Group II (H) seven out of eleven that did not bleed until after the third ulcer year, whereas in Group I (H) most followed the usual course by getting into trouble during the early years of their ulcer. Emory and Monroe⁷ feel that the highest incidence occurs in the first two years of the ulcer history, thereafter dropping off. In Group II (H) the ulcers were old ones which are generally considered

group was unnecessary. Had the diagnosis been made sooner, and proper ulcer treatment initiated, the subsequent complication might have been prevented. It is certainly one further example to indicate that the gastrointestinal complaints of the diabetic should be heeded carefully, especially in the mild diabetic, since we have seen that, with few exceptions, this series is made up of the case which is easy to control, and should have no reason for abdominal discomfort unless it is due to some cause other than diabetes.

Radical surgery was performed to cure multiple bleeding in one, acute massive hemorrhage in another. One other multiple bleeder was operated, but in this case the operation was performed for a recently developed gastrojejunocolic fistula. Subtotal gastric resection was done in all with no post-operative deaths.

PERFORATION

Perforation occurred in ten cases (10.6%). In all, we observed a total of thirteen perforations: two cases had two or more. One individual suffered an acute episode and underwent gastroenterostomy prior to the onset of diabetes. Later he developed a gastrojeuno-

colic fistula. In addition to the symptoms referable to this he complained of severe back pain. Surgery revealed a gastric ulcer of the lesser curve, a posterior duodenal ulcer which had perforated into the pancreas, and the ulcer responsible for the fistula. The other case had an anterior gastric ulcer which perforated acutely. Following primary closure he had an uneventful recovery. Subsequently he was operated again for a persistent retention of 85%. A subtotal resection was done, and the specimen revealed a posterior wall gastric ulcer eroding the pancreas, the anterior gastric, which had perforated prior, and a chronic duodenal ulcer.

ACUTE PERFORATION

Four acute perforations occurred in the entire group. Two of these, however, had taken place before the onset of diabetes, so actually we have seen only two diabetics who have suffered this complication. One of

in addition to the duodenal ulcer which had caused the bleeding, three others, one duodenal and two gastric, one of which was perforating.

GASTROJEJUNOCOLIC FISTULA

This complication was present in three cases. The first symptoms referable to a fistula were experienced nineteen, ten, and nine years following the gastroenterostomies done. In each case the trouble first began after the onset of diabetes, but they had all had the latter for five years or more. Surgery was performed in two.

COMMON DUCT DUODENAL FISTULA

One common duct duodenal fistula was found in a patient who was admitted for acute obstruction. He had been told five years previously that such a condition existed, but refused surgical treatment on the grounds that he had not had much trouble yet.

TABLE IV-b, GROUP II(H)						
First hemorrhage in ulcer history, gross or massive	Second hemorrhage in history	Total No. of hemorrhages	Arteriosclerosis	Blood pressure	Duration D. M. at 1st hem.	Duration ulcer at onset D. M.
15th year	17th year	2	Gen. A. S.	205/110	10 years	5 years
1st year	2nd year	MX	Gen. A. S.	160/80	—	14 years
8th year	0	1	Grade 1	112/80	5 years	3 years
7th year	0	1	Grade 1	130/100	6 years	1 year
1st year	0	1	Grade 2	132/76	½ year	1 year
10th year	11th year	2	Gen. A. S.	145/90	1 year	9 years
2nd year	0	1	Grade 1	105/80	1 year	1 year
4th year	6th year	MX	Gen. A. S.	124/80	2 years	2 years
10th year	0	1	Grade 2	120/70	7 years	3 years
1st year	0	1	Grade 1	176/80	—	8 years
5th year	8th year	MX	Gen. A. S.	180/90	—	7 years
Occult blood only						
7th year	0	1	Gen. A. S.	200/130	6 years	1 year
15th year	0	1	Gen. A. S.	136/70	2 years	13 years

the cases, a 71-year-old male, was admitted to the hospital with an undetermined diagnosis approximately thirty-six hours after the onset of his illness, and after having traveled many miles from a small town in Vermont. He rapidly developed renal failure and died soon after admission. The other acute perforation in a diabetic is the last case mentioned in the first paragraph of this section.

CHRONIC PERFORATION

One chronic perforation with a subdiaphragmatic abscess was seen in a 70-year-old female who had a gastric ulcer. She was operated and the abscess drained with uneventful recovery.

SUBACUTE PERFORATION

Surgery revealed that subacute perforation had occurred in four cases. Three were observed to have eroded into the pancreas. Two have already been mentioned in the first paragraph. The third case was one that was operated to stop a persistent severe hemorrhage. This case also had two ulcers; the duodenal which was the cause of the bleeding had perforated into the pancreas, and a chronic gastric ulcer of the lesser curve. The diagnosis of subacute perforation in the fourth case was made from the surgical specimen in the pathology laboratory. This man had been operated for recurrent hemorrhage. The specimen showed,

Complications occurred in these people at an average age of 61.6 years. The ulcers had been present an average of 6.0 years. This figure includes the fistula cases. If we exclude them, we would have an average duration of ulcer of 2.28 years. This is in accord with Dwyer, Blackford, Cole and Williams⁶ who feel that more perforations occur in the early stages of the ulcer.

Six cases that perforated also had a history of one or more gross hemorrhages. Three others later had trouble with retention. One, in fact, has had hemorrhage, perforation and obstruction. He is the one with the common duct duodenal fistula who refused surgery.

Summarizing, it is seen that gastric ulcer was responsible for the complication in three instances, duodenal in four. Surgical specimens have shown multiple ulcers to be present in five individuals of this group.

For some reason unknown to us, but probably coincidental, all but one of these people have had an unusually virulent type of ulcer diathesis, which has caused more than one type of serious complications to occur in the same person. The high incidence of multiple ulcers may be the explanation. However, it is likely had we been able to see the stomachs and duodenums of the others in this series, we would have found multiple ulcers to be more frequent in them too.

The incidence is low for acute perforations, but if we take into consideration the fact that more than

one-third of this series are people in Group II, who have had ulcers an average of 11.5 years, and if we accept the theory that more ulcers perforate in the early stages, then it is reasonable to assume that this factor has had something to do with bringing the incidence down. In Group I the two cases observed make an incidence of 3.4% which is not too low to lose significance.

Each group is represented by five patients.

OBSTRUCTION

Retention was the greatest single cause for trouble in this series. In thirty-two cases the clinical impression, as determined by history, and gastric aspiration, was supported by X-ray evidence of retention in various degrees. Twelve females and twenty males made an incidence of 34.0% of all the diabetics with ulcers who were seen at the George F. Baker Clinic during the eleven-year period of this study.

The complication was due to a single gastric ulcer in three instances, one of which had hour glass contraction. Twenty-five were the result of single duodenal ulcers, and in three cases obstruction occurred in patients who had coexistent gastric and duodenal lesions. Cicatricial contraction occurred in one patient from a peptic ulcer in the lower third of the esophagus.

Twenty-seven (84.4%) of this group were forty years or more old. The average age at the onset of ulcer symptoms was 49.7 years, and 54.6 years at the time of obstruction. This makes the average duration of the ulcer 4.9 years when the trouble began. Nine cases had symptoms for five years or more—only 28.1% of the retention group—a decided contrast to Jordon and Kiefers' series where 68% had their ulcers more than five years. In the remainder of the group, ten got into trouble during the first year, six in the second, three in the third, and four in the fourth.

In the obstructed group twenty-two cases (68.75%) were observed that had a retention of 30% or more. Nineteen of the twenty-two had figures ranging from 40% to 100%. Six patients had retention from 15% to 25%, while only two had an estimated residue of 10%. No percentage estimate was made in the esophageal ulcer.

Surgery was necessary in 18.75% as contrasted to Jordon and Kiefer's series where 11.0% required surgery. A posterior gastroenterostomy was performed in one duodenal ulcer. Subtotal gastrectomy was done for three duodenal, one gastric with hour glass contraction, and one case with combined gastric and duodenal ulcers. In no case was surgery attempted where the retention was less than 40% after a good medical trial. No surgical deaths occurred.

Medical management was successful in twenty-six cases, 81.25%.

Unlike the perforation group where two cases complicated before the onset of diabetes, all the people here had diabetes at the time of the obstruction.

When the obstruction cases were separated into two groups it was found that retention played its biggest role in the people of Group I. As before, we will

refer to the complicated cases from each group as Group I(O) or Group II(O).

GROUP I(O)

40.7% of all the people who developed an ulcer after they had diabetes for various periods became obstructed at some time during the course of their new disease. Twenty-four cases comprised 75.0% of all the patients with retention.

The average age at onset of ulcer symptoms was 54.5 years. They became obstructed at an average age of 57.25 years. 2.75 years was the average duration of the ulcer. Only three cases had their ulcer for five or more years when they got into trouble. This is 12.5% as contrasted to Jordon and Keifer's 68% with symptoms longer than five years duration. Three became obstructed in the fourth year, three in the third, five in the second, and ten in the first.

75.0% of Group I(O) had retention of 30% or more. The eighteen cases formed 81.8% of those in the entire obstructed group who had a retention of 30% or more. Fifteen of the eighteen above had a residue of 40% or more and make 62.5% of Group I(O). An estimate of 15% to 25% residue was found in four, 10% in one.

Surgery was required in five patients (20.83%). Subtotal gastric resection was done in all the surgical cases from Group I(O).

Table V-a gives the complete data on the duration of ulcer, degree of retention, and duration of diabetes in each case from this group.

Group II(O)

Group II(O) is represented by eight patients who formed 25% of the obstructed group, but only 22.58% of the thirty-five cases in their own group.

All eight were more than fifty years old with an average age at obstruction of 56.37 years. Symptoms of ulcer had been present an average of 11.5 years. In six cases the ulcer had been present for five years or more. This is 75% with symptoms five years or more and it compares well with Jordon and Kiefer's 68%. One obstructed in the fourth year, one other in the second.

The estimated retention was 40% or more in four cases, 15% in two, and 10% in two. The response to medical management was generally better in this group. Surgery was necessary in only one, 12.5%.

Table V-b shows the relationship of the onset of diabetes to the onset of obstruction. Two patients are outstanding here in that they had ulcers for long periods of time, but did not get into trouble until shortly after the onset of diabetes. One of them, in fact, had a thirty-nine year remission until he was being treated for diabetes, whereupon symptoms became apparent again, and inside of two years he had x-ray evidence of 50% retention. The other case had an ulcer which had been quiet for ten years. He had a remission the first year of his diabetes. Another case, the second one in Table V-b, came into the hospital with an undiagnosed duodenal ulcer which had given mild symptoms for two years. On admission she had nausea

and vomiting with vague abdominal pain. It was thought at first to be a pre-coma state, but blood sugars done immediately ruled this out. A G. I. series taken later revealed the presence of a duodenal ulcer with a gastric retention of 15%.

sequent obstruction had developed after long remissions. This would indicate that peptic ulcer in a diabetic can be a more serious disease, particularly in one of long standing who develops an ulcer and sticks to his habitual diet in spite of the mild abdominal symptoms which he has.

The obstructed cases in Group I(O) are excellent examples to show where the habits formed from long association with one disease has had an effect on the eventual course of the other. Let us consider what the average diabetic knows about his disease and its treatment. He knows that hunger and abdominal pain can be a manifestation of too much protamin zinc insulin. He also knows, if the urine contains sugar, that these same symptoms can be caused by uncontrolled diabetes. If he has had diabetes very long, he will have developed the habit of first blaming all of his ills on either one or the other. Since he does not truly understand the symptoms from a recently developed ulcer, it is more than likely that he will attribute them to his diabetic state either in the form of a P. Z. I. reaction, if the urine happens to be sugar-free, or to uncontrolled diabetes, if he is one who has neglected himself and is just now checking up to see. In the first case, he attempts to adjust himself by lowering the insulin dose or cutting it out entirely. Usually he eats more, too. Soon he is out of diabetic control. He doesn't feel any better, and becomes similar to the second patient who will raise the insulin and attempt to control the glycosuria by further dietary restrictions which include many five per cent vegetables and other rough foods. Very likely if any retention is developing, he will have had some pretty bad reactions from insulin because food taken in is either not absorbed or vomited. Finally, our diabetic really becomes confused and consults a doctor, who also may find the case puzzling because of the vague symptoms which are easily confused with similar ones resulting from diabetes or its treatment, and are so common. Such a situation is apt to cause enough delay in the diagnosis and treatment of a newly acquired ulcer which could lead to complications.

In this light, let us consider Group II. Many of these people had had ulcers diagnosed and treated before the onset of diabetes. In general, when symptoms recurred they were in a much better position to understand them. They were not so apt to be faithful to their diabetic diets, and usually consulted a doctor sooner. Despite this the incidence was higher than it should be (22.58%), but it nowhere near compared with that of Group I. Here, too, in many cases, especially the long remission ones, the symptoms tended to be confusing both to the patient and the doctor.

In no way were we able to demonstrate that some intrinsic factor in the nature of the ulcer or the diabetes was responsible for this high incidence. The symptoms prior to obstruction were not different from the rest of the group; the acid values were not remarkable. To date we have observed no instance where obstruction has recurred. Those who responded well to medical treatment have continued to be fairly well off, as have the surgical cases. Subsequent follow-up

TABLE V-a, GROUP I(O), DURATION ULCER AND DURATION D. M. AT OBSTRUCTION

Duration ulcer at obstruction	Duration D. M. at obstruction	Percent retention
13 years	14 years	40
1 year	3 years	40
6 years	15 years	70
6 years	21 years	40
2 years	7 years	25
4 years	15 years	60
1 year	4 years	35
1 year	1 year	40
1 year	14 years	30
2 years	7 years	10
1 year	21 years	35
1 year	4 years	70-S
4 years	7 years	100-S
1 year	2 years	20
3 years	11 years	50-S
2 years	20 years	90-S
1 year	18 years	40
1 year	2 years	85-S
3 years	13 years	20
2 years	15 years	85
2 years	10 years	40
4 years	5 years	—
		(esoph. ulcer)
3 years	14 years	15
1 year	12 years	40

TABLE V-b, GROUP II(O)

7 years	7 years	15
2 years	1 year	15
10 years	1 year	60
4 years	2 years	40-S
20 years	11 years	10
39 years	2 years	50
5 years	5 years	10
5 years	4 years	90

S = Surgical case.

From the figures shown, it is apparent that in Group II(O) the cases have approached the closest to what one would expect. The incidence is high, but in respect to Jordon and Kiefer's on age, duration of ulcer, and response to treatment, it compares very well with their group. If we can exclude the four in which we felt the onset of diabetes played a part, we would have an incidence of 11.4% in Group II(O) which compares well with Portis and Jaffe's¹⁰ incidence to 11.6% taken from autopsy material, and Emery and Monroe's¹¹ 11.7% taken from clinical material.

Reviewing the data, we see that obstruction was the most important cause of symptoms in this series, and that the incidence and seriousness in Group I(O) was most marked. When we consider that Group I formed 62.7% of the entire ninety-four cases, and find that the obstructed cases in this group make up 75% of the total retention series, 81.8% of those with 30% retention or more, and 83.3% of the surgical cases, it seems apparent that some factor is at work which is causing this high morbidity. In addition, we find that many of these Group I(O) ulcers have caused trouble in a relatively short time. Also, we saw two instances in Group II(O) where, soon after the onset of diabetes and its treatment a recurrence of symptoms with sub-

studies, and more new cases as time goes by, may prove that the rough diet of a diabetic on an undiagnosed ulcer has been the single causative factor.

CARCINOMA

Carcinoma of the stomach was found in three cases. In one a definite diagnosis of cancer developing in a chronic gastric ulcer was made by the pathologist. This case had been operated because primary ulcerating carcinoma was suspected. It was a surprise to find a chronic ulcer the cause of symptoms. Following surgery he had post-operative obstruction and peritonitis which caused his death. The second patient had suffered from a chronic gastric ulcer for years. Shortly before the last admission he began to have symptoms again, and on several occasions vomited blood. He had lost a few pounds of weight. An x-ray revealed a new lesion in the cardia of the stomach. A similar history was obtained in a third man who subsequently developed a primary gastric carcinoma after having had a chronic gastric ulcer for a long time.

DISCUSSION

The age of the patients seen in this series was greater than one would see in an average ulcer group. The onset of diabetes generally occurs in people during the middle stage of life, or past, and this can account for the older age of the majority of the patients in this report. The relatively high incidence of female patients can also be explained by the actual higher incidence of diabetes among women.

One acute ulcer was seen. The diagnosis was made in the pathology laboratory from a surgical specimen. Surgery revealed multiple ulcers in five of the eight coexistent gastric and duodenal ulcers known to be present. In each case the presence of additional lesions was unsuspected, thus hinting that the actual incidence for multiple ulcers may have been higher than 8.5% as found here.

The vagueness of initial symptoms was the most unusual finding in this series. Many single factors could be the explanation, but a combination of them is the most likely. The age of most people in this series undoubtedly played a big part. Dwyer, Blackford, Cole and Williams¹² pointed out that there was a gradual decline in typical symptoms as age increased. Second, the pain of an uncomplicated ulcer seems to be associated with the amount of free hydrochloric acid. Emery and Monroe¹³ have stated: "We have observed no instance in which an ulcer gave characteristic symptoms in the absence of F.HCL." In that paper two cases were cited which had typical x-ray evidence of duodenal ulcer. One was a patient with pernicious anemia; another had osteitis deformans. Both had achlorhydria, but no ulcer distress. In a non-diabetic ulcer group advanced age with its corresponding decline in gastric acidity might well be the explanation for atypical symptoms. In this diabetic series, however, cases were seen in the younger group where the symptoms should have been typical, but were not. Apparently diabetes has had something

to do with this. It was shown that the symptoms were most atypical in Group I, the patients who had diabetes the longest. Also, the acidity values were lower in this group. Root¹⁴ had reported achlorhydria in 30%-40% of diabetic people, and noted that the incidence of achlorhydria became greater with the longer duration diabetes, and also with age. Bowen and Aaron¹⁵ have made similar observations. Dibold¹⁶ has shown the degree of gastric acidity to be affected by the level of the blood sugar, and illustrated that the effect of insulin in lowering the blood sugar was associated with a corresponding rise in gastric acidity.

Table VI gives complete data on the relationship of pain to age, acidity, and duration of diabetes. In general, the data indicates that all the factors have played a part in the symptomatology of these ulcers.

Another important consideration is to be found in diabetic dietary habits. Many patients, especially those receiving protamin zinc insulin, are advised to take a small glass of milk and a cracker at bedtime and between meals. This habit in itself could do much to prevent the manifestation of pain associated with an empty stomach.

Complications were present in an unusually high per cent. The part a rough diabetic diet may have played has been considered, but it is more than likely that vagueness of symptoms was the greatest factor to begin with, allowing many to go undiagnosed and untreated for considerable periods of time. This point is illustrated very well by the diabetics in Group I where the symptomatology was more vague and a high percentage obstructed soon after the onset of ulcer symptoms. Any food, even that from a diabetic diet, will tend to relieve ulcer distress, but the mechanical effect is present none the less, and an ulcer thus insulted can not go long without causing trouble.

It is possible that arteriosclerosis had something to do with subsequent complications. Tissues in arteriosclerotic individuals are not so apt to heal as quickly or well as those in people with healthy arteries, and this may have contributed somewhat to the outcome. It may or may not be important, but at any rate arteriosclerosis certainly has an effect upon the prognosis in a bleeding ulcer, and this alone makes it a subject for serious consideration in a diabetic more than any other individual.

Advanced arteriosclerosis was seen to be present in most of the troublesome bleeders, and it was shown that the most serious bleeding occurred in Group I where the incidence for A. S. was the highest, and the duration of diabetes the longest. In the entire series forty-two cases were determined to have had generalized arteriosclerosis—enough to make such a finding unusually common in any group, but when 76.2% of the advanced cases were found to be from Group I, it is an outstanding thing, and indicates that age alone was not the only factor working to bring the incidence up. The presence of arteriosclerosis is actually much higher even than this figure indicates, for in no instance so far has the duration of the diabetic state been taken into consideration when an estimate of the

degree of A. S. was made. This must be done when one considers the condition of the arteries in a diabetic, "A diabetic of ten years' duration can generally be assumed to have an advanced degree of arteriosclerosis¹⁷." And this is regardless of the age group to which they belong. The condition of the radial artery has been used in a previous section of this paper to indicate degrees of arteriosclerosis other than the generalized one. In general this method is not a satisfactory one. In diabetics it is less so. Seven of the fourteen who had no gross or other evidence of arteriosclerosis had diabetes for ten years or longer. Taking everything into account, very few patients in this entire series had arteries that could be considered young.

The subject has been brought up here only to point out that in many cases serious arteriosclerosis can exist in young diabetics of long duration where it is least expected, and could possibly have an effect on the prognosis of an ulcer in such a person. These people should not be considered young. Physiologically they belong to the older age group—as is indicated by the high incidence of acute coronary deaths in long duration young diabetics—where ulcers have a higher mortality and morbidity rate, especially those that bleed.

The possible effect of this type of arteriosclerosis on the prognosis of an ulcer is purely theory. Unfortunately, this series is small, and no case is available to illustrate the point. However, with more and more young diabetics growing up to enter the ulcer age, time will prove whether the assumption is correct or not. Until then, it would be best to consider every diabetic of long duration with peptic ulcer as a potential massive bleeder.

Diabetic coma subsequently developed in seven people, and as is usually the case, could have been prevented. It is true that the diabetic state was more severe in these individuals, and symptoms from the ulcer more prominent, but an alert patient would have detected the warning glycosuria, and taken the necessary steps to prevent acidosis. Actually eighty-five patients who were classified mild or moderate in this report should present no problem in diabetic control. The insulin requirement may change from time to time, but daily urine exams will detect this, and the patient can adjust the dose accordingly. The five comas in Group II are additional examples illustrating where the habits derived from long association with one disease has influenced the course of the new one. They just ate too much, treating their ulcer often, but not too well; for coincidently with coma, three of these had large degrees of retention which required long periods of medical management for relief. A large gastric residue and vomiting is a common occurrence in acidosis. In the three mentioned, however, the presence of an ulcer was known, and further observation proved it to be the cause of the retention.

Gastric aspiration and lavage with a few days on a low residue bland diet is a routine procedure for acidosis at this clinic. It is also a good one for an ulcer, and it may be in a few cases among the many dia-

betics who are admitted with mild acidosis, nausea and vomiting, that an ulcer causing a low grade obstruction has been overlooked. Most cases of this type would respond pretty well on the treatment given for coma alone, and in a few days feel so much better that the possibility is not considered.

The incidence for peptic ulcer in this series is low—

TABLE VI, RELATION OF F.HCL, PAIN, AGE, AND DURATION OF D. M.

Fasting F.HCL	Rise to	Pain	Age group	Duration D.M. yrs.	Group
0	38	1	6	15	I
63	65	1	3	9	I
42	58	1	5	17	I
35	70	0	5	26	I
18	40	1	5	18	I
70	70	1	6	15	I
0	40	1	6	21	I
0	0	3	4	15	II
4	56	1	3	5	I
11	43	2	4	9	II
35	42	2	4	1	II
3	48	3	5	4	II
36	120	3	2	8	II
0	38	2	6	15	I
11	42	1	4	7	II
27	60	1	6	11	I
20	51	1	3	4	I
29	29	1	5	6	I
12	70	2	4	6	II
28	28	2	5	14	I
52	52	3	4	5	I
27	37	1	4	14	I
0	tr.	2	3	12	I
4	tr.	2	5	1	II
0	32	2	5	2	I
0	16	3	3	1	I
6	50	2	4	10	I
0	14	1	4	1	I
4	77	2	4	3	II
0	10	1	3	13	I
0	0	2	5	4	I
0	60	2	3	6	II
0	0	2	5	21	I
58	116	2	5	5	II
26	88	3	4	11	II
0	25	2	6	9	I
0	20	2	3	2	I
20	43	2	5	12	I
0	6	1	4	6	II
38	38	1	5	20	I
20	52	1	4	4	II
0	4	2	4	16	II
16	46	2	4	2	II
0	68	1	7	9	II
60	70	2	6	2	I
10	34	1	5	13	I
6	16	1	2	5	II
18	52	1	5	4	II
18	86	1	3	2	II
64	90	1	4	13	I
30	52	1	5	12	I
0	24	1	7	19	II
0	13	1	4	2	II
38	73	1	7	6	II
0	0	1	7	14	II
14	69	1	7	13	II
0	0	1	7	25	I
30	84	1	6	6	II

KEY TO TABLE VI

Pain classified as follows—

- 1—Vague, indefinite.
- 2—Definite time relationship, localized, periodic.
- 3—Severe enough to wake at night.

Age classification—

- 2—20 to 29 years.
- 3—30 to 39 years, etc.

0.78%. Other¹⁸ reports have indicated a low incidence also. But can this be a true indication of the actual incidence? With the symptomatology vague as it was in many cases, we begin to wonder how often the diagnosis has been missed.

In the face of low acid, age, and ill-defined symptoms the question of malignancy is going to come up more often in the diabetic. As in many cases of this nature, the diagnosis will be difficult to establish, but it will be thought of more often, and it is the only instance where a diabetic is liable to benefit by his unusual symptoms.

THERAPEUTIC MANAGEMENT

In every case the treatment was primarily directed toward the management of the ulcer, controlling the hyperglycemia and glycosuria with insulin. It was seen that the diabetes in the majority of cases was mild thus making the problem much simpler. Even in the more severe diabetics, however, a program so directed has been quite satisfactory.

It is necessary to provide a well-balanced diet of CHO, fat, and protein suitable to the diabetic state, but any type of diet required for the management of an ulcer at any stage can be calculated so that it will be a good one for both diseases and at the same time provide all the calories necessary. Table VII gives four such diets. But any attempt at standardization should be avoided for every diet should be figured according to the specific requirements of each individual, taking into consideration his metabolism, type of work, and present weight, and adjustments made accordingly. Additional vitamins should supplement each diet.

A diabetic temporarily out of control may at first seem to be a severe one requiring large doses of insulin. After a period of vigorous treatment the insulin dose necessary for adequate control will usually drop and remain fairly constant at a much lower level. A knowledge of the previous amount of insulin required for each patient is helpful so that some estimate can be made. If a person on a previously well-regulated diet continues to need much more insulin than usual, it will probably indicate some focus of infection is causing it, and, if he has an ulcer it might well be that a sub-acute of chronic perforation is the cause. Conversely, if a person should begin to have insulin reactions on a dose previously suitable, think of retention. It may be developing.

In the more severe diabetic states it will sometimes be necessary to give additional crystalline insulin at 11:00 A. M., 4:00 P. M., and 10:00 P. M., according to the color of the Benedict test. For example: If the test is red, give sixteen units; orange, twelve; yellow, eight; green or blue, none. This, too, may vary according to the individual. Some cases will be found where six or eight units is enough for a red test, while others may require as much as twenty-four.

In the face of an obstruction the diabetic state will be harder to manage and the use of insulin may lead to bad reactions because of vomiting and the undependable

absorption of food. Insulin also tends to increase the gastric motility thus contributing to the subjective symptoms of the patient. The diabetes will have to be watched more closely, but here, too, the aim should be to consider the ulcer first, making adjustments for controlling the diabetes the best we can under the circumstances.

The nutritional factor subsequent to faulty absorp-

TABLE VII

(All dietary prescriptions in grams)

MODIFIED SIPPY DIET C-138, P-66, F-110

Milk	-----30 cc.	7-9-11-1-3-5-7-9-11
Cream	-----30 cc.	
8 A. M.	-----15 cereal 60 cream	
10 A. M.	-----One egg 30 toast 5 butter 50 strained orange juice	
12 Noon	-----cream soup 180 unecdas 2	(C-12, P-6, F-8)
3 P. M.	-----cottage cheese 45 unecdas 2	(P-9)
6 P. M.	-----milk toast warm milk 180 toast 30	
9 P. M.	-----unecdas 2 BK custard 120 (120 milk, $\frac{1}{2}$ egg, 5 sugar)	(C-11, P-7, F-7)

CONVALESCENT ULCER C-161, P-75, F-95 Calories 1799

Breakfast	-----one egg, 15 oatmeal, 20% cream 60, milk 120, cooked orange juice 100, bread 15
Dinner	-----ground meat 60, 10% vegetables 90, butter 10, 20% cream 30, cooked orange juice 100, po- tato 60, bread 15
Supper	-----same as dinner
Between meals	-----120 milk, 2 unecdas morning, afternoon and night.

BLAND DIET C-149, P-41, F-55 Calories 1255

Breakfast	-----oatmeal 15, butter 5, 20% cream 60, milk 120, cooked orange juice 100, bread 15.
Dinner	-----cream soup 180, butter 5, cooked orange juice 150, potato 45, bread 30.
Supper	-----one egg, butter 5, milk 180, cooked orange juice 150, bread 30.
At bedtime	-----120 milk, 2 unecdas.

BLAND DIET C-203, P-73, F-86 CALORIES 1878

Breakfast	-----oatmeal 15, butter 5, 20% cream 60, milk 120, cooked orange juice 100, bread 30.
Dinner	-----2 eggs, cream soup 180, butter 5, milk 180, cooked orange juice 150, potato 60, bread 30.
Supper	-----milk toast (warm milk 180, bread 45), butter 5, cooked orange juice 150.
Between meals	-----morning—eggnog (180 milk, 1 egg, no sugar); afternoon—2 unecdas, cream cheese 15; night— milk 120, unecdas 2.

tion or vomiting of ingested food is important to the diabetic who needs all the nourishment that his diet will provide. A long medical regime will be a definite disadvantage to the diabetic who subsequently is going to need surgery for relief. Medical management will give good results in most cases, but when faced with a definite high-grade obstruction at the outset, do not hesitate to advise surgery for there is no reason why

these people can not be treated the same as others with similar complications.

Following surgery the management can be the same in every way to the post-operative course prescribed for the usual subtotal gastrectomy of gastroenterost-

omy. All one needs to do is figure a diet with the proportion of CHO, fat and protein suitable for the diabetic, and follow them closely from day to day with frequent blood sugars taken fasting, and at eleven A. M. or four P. M.

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Colloidal Aluminum Hydroxide Gel and Magnesium Hydroxide in the Management of Peptic Ulcers

By

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FOR OVER 25 years the Sippy management dominated the medical treatment of gastro-duodenal ulcers. Briefly stated, this method depends upon frequent feedings of bland, non-irritating foods and the administration of alkalis to neutralize the gastric acidity. As originally described by Sippy¹ the method attempts to neutralize completely all gastric acids during the day and night. The diet is graded from milk and cream every waking hour to a fairly well-balanced one within four or more weeks, when a six-meal diet is given. As experience with this management accumulated many modifications were introduced but the principles have stood the test of time. Gradually, many drawbacks have become recognized. The acid rebound is the chief difficulty in the Sippy management of peptic ulcers. Alkalosis, the result of excessive amounts of alkalis administered in this treatment occurs in two to five per cent of the cases. In post-hemorrhage cases the alkalis interfere with the proper absorption of orally administered iron and thereby delay the restitution of the blood. Occasionally, renal stones² develop as a complication of the Sippy regime.

In 1934 Einsel, Adams and Myers³ introduced colloidal aluminum hydroxide gel as an alternate to the alkaline powders in the Sippy management of gastro-duodenal ulcers. Since this drug is not absorbed the danger of alkalosis from this source is eliminated. The acid rebound is greatly diminished or completely obliterated with the judicious use of this preparation and the complication of renal stones is avoided. This drug is also supposed to inactivate the pepsin⁴. In our experience colloidal aluminum hydroxide gel in therapeutic doses does not interfere with the absorption of

iron. Hence, there is no delay in restitution of the hemoglobin in bleeding cases. Thus, with the substitution of colloidal aluminum hydroxide gel for the alkalis of the Sippy regime practically all the drawbacks of the latter drugs are eliminated.

The efficiency of the aluminum gel to adsorb hydrochloric acid is proven by the simple in vitro experiments reported below. Its clinical efficacy in controlling ulcer pain and heartburn is well known. However, the chart below shows that under controlled conditions the different brands of this preparation vary considerably in their neutralizing power. Fairly large doses must be given at frequent intervals to get a therapeutic effect. One of the side effects of this drug is its tendency to produce constipation. Since most of the ulcer patients have such a tendency it aggravates the constipation and rarely produces obstipation or rectal impaction, particularly in bed-ridden patients. There have been reported cases of intestinal obstruction caused by colloidal aluminum hydroxide gel.

Another consideration, though entirely theoretical, deserves mention. The aluminum hydroxide adsorbs phosphates and hence may cause a diminution of the blood phosphates. Since the usual ulcer diet is high in this element this objection to the drug is more theoretical than actual and in practice may be ignored. Recent studies by Hoffman and Dyniewicz⁵ show that aluminum hydroxide gel interferes to a minor degree with proper absorption of vitamin A. However, that, too, is of no practical consideration since very adequate amounts of this vitamin are present in the routine ulcer diet. The same authors⁶ show that this drug in therapeutic doses has no demonstrable effect upon the absorption of the nutrient substances studied (amino

acids, ascorbic acid, glucose and neutral fat). Thus, the most important disadvantages of colloidal aluminum hydroxide gel in the management of peptic ulcer are, first, the lack of uniformity of the preparations in their adsorptive power and, second, the constipating effect.

To overcome both difficulties the writer has used for the last two years a combination of a colloidal aluminum hydroxide gel of high adsorptive power in combination with four per cent magnesium hydroxide. The results in over 150 ulcer cases are rather gratifying in that pain and heartburn are controlled with smaller and less frequent doses of this combination and without producing any disturbing by-effects. At no time was an acid rebound demonstrated. The constipation which is often present in patients who have a peptic ulcer, is controlled by this preparation in most cases. In no case is it aggravated. In fact, in a few instances a mild and transient diarrhea develops. As far as could be determined from clinical observations this preparation does not diminish the absorption of therapeutically administered iron in post-hemorrhage cases.

The preparation is stable, though on standing a settling of the gel occurs, which is readily eliminated by a few shaking motions. The adsorptive power of this combination is uniform and does not appear to diminish with age. The taste of it is rather flat, but not unpleasant. The addition of a very minute quantity of peppermint improves the taste and does not alter its therapeutic effect.

The combining power of this combination as compared to three popular brands of colloidal aluminum hydroxide gel can be determined by the following simple in vitro test. The U. S. P. xii test for acid adsorption was used as standard of comparison. Eight cc. of the preparation was tested.

Aluminum hydroxide gel			Aluminum hydroxide gel and magnesia hydroxide
Product A	Product B	Product C	
Adsorbs	Adsorbs	Adsorbs	Neutralizes
120 cc.	120 cc.	176 cc.	196 cc.
n/10 HCL	n/10 HCL	n/10 HCL	n/10 HCL

This shows that the last preparation is 12.5 per cent more efficient than one brand and 62 per cent more efficient than two brands of alumina gel. It also shows the variability of the alumina gel preparations sold under trade names.

The experimental observations of Rossett and Flexner⁷ show that the combination of colloidal aluminum hydroxide gel and milk of magnesia acts as an effective buffer for over two hours without carrying the (gastric juice) ph above the upper limits of the physiological range. Therefore, this combination results in more prolonged effect than colloidal aluminum hydroxide gel with the subsequent necessity of smaller and less frequent doses. The undesirable initial rise in ph resulting from the use of milk of magnesia alone is avoided.

In our experience 8 cc. of this combination three or four times a day together with a proper diet is adequate to give a patient relief from pain and heartburn in most uncomplicated peptic ulcers and in many instances with a partial pyloric obstruction. No objection could be found to this combination in post-hemorrhage cases. When indicated, it can be used for long periods without the fear of alkalosis, of acid rebound or of aggravation of the constipation.

When the patient becomes symptom-free the same combination can be used when and as needed. This preparation is also suitable for a continuous drip treatment of peptic ulcers.

SUMMARY

Colloidal aluminum hydroxide gel and magnesium hydroxide combination is an effective stable buffer which acts in the stomach for several hours. With this combination ulcer pain and heartburn may be controlled with smaller and less frequent doses than are required with the colloidal aluminum hydroxide gel alone. Clinically it can be continued for long periods without the danger of an acid rebound, alkalosis or aggravation of constipation.

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Regional Colitis Involving the Descending Colon and Sigmoid

By

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MANY AUTHORS have substantiated the belief that regional ileitis is a phase of a chronic inflammatory disease of unknown origin, which does not only elect and affect the ileum, but may involve the cecum and other segments of the colon¹. The lesion may affect additionally the jejunum and ascending colon by continuous "spread," or with intervening areas of normal bowel interposed (skip areas).

Generally the term "segmental enteritis," first introduced by R. Lewisohn in 1938², seems to be a more appropriate descriptive name for this process when it involves two or more segments of the bowel. The designation "regional enteritis" (Brown) or regional colitis would be more descriptive of those cases where only one section of the bowel is involved. The fact is that many cases of recurrence of this process in another section of the bowel do occur, even after the diseased portion has been removed³⁻⁴. Crohn modified his original concept in 1938 when he expanded this disease to include the entire intestinal tract⁵. Attention is here directed to the comparative rarity of this process occurring in the sigmoid and descending colon. In 1930, Bargen and Weber⁶ reported a series of 23 cases in which the transverse colon and descending colon were mainly involved in the pathologic process. Cases 3, 5, 9, 10 and 22 included the sigmoid. Cases 20 and 21 involved the entire colon. In 1934, Brown et al⁷ reported a series of 18 cases of regional enteritis involving the following distribution: 9 cases in the ileum, 3 in the jejunum, 1 in the terminal ileum and a small portion of the cecum, 5 in the ileum (terminal) and a part of the ascending colon. Shapiro⁸ in his review of 261 collected cases of regional ileitis noted one single instance of involvement of the sigmoid and descending colon reported by Dalziel in 1913⁹. In the 21 cases reported by Bockus¹⁰, 9 cases involved the ileum and colon in the following proportions: 7 cases involved the terminal ileum, proximal colon to the sigmoid, 1 case involved the terminal ileum and cecum, 1 case involved the terminal ileum, ascending colon, and splenic flexure (skip areas).

In Sneider's series of 22 cases of regional enteritis, 14 underwent resection. Only 1 case, in a man 47 years old (case No. 8), involved the sigmoid only¹¹.

It occurred to us that extensive involvement of the descending colon and sigmoid in an apparently otherwise healthy man of 65 years of age, who showed no evidence of involvement of "skip areas" in other segments of the colon, either preoperatively or two years

postoperatively, was sufficiently rare to warrant reporting.

E. K., referred by Dr. B. Zamostein, 65 years of age, a jeweler by occupation, was admitted to the Mt. Sinai Hospital on July 25, 1944, complaining of intermittent attacks of abdominal pain. He apparently enjoyed good health until early May, 1944 (two months before admission), when he started to complain of lower abdominal pain associated with from 8 to 12 watery stools containing considerable mucus and only rarely blood. The pain varied from a dull ache across the lower abdomen, to a generalized, sharp cutting type of pain. The latter would come on intermittently and especially after the ingestion of food. The duration varied from half an hour to as many as several hours after meals. As the condition progressed, the pain became more severe and seemed to localize in the area of the right lower quadrant and in the rectum. He lost 15 pounds since the onset of the condition. His appetite became very poor and he feared to eat because of the subsequent pain. One week prior to his admission he was compelled to go to bed. An x-ray taken at this time, was reported as a probable ulcerative colitis. Proctologic examination visualized a stenosing mass within the lumen of the bowel five inches from the rectum, the exact nature of which could not be defined. Since the condition did not improve, he was hospitalized. His past history was significant in that he never had gastro-intestinal complaints. He was only occasionally constipated and never noted changes in bowel habit until the present onset. He had a mild attack of typhoid fever in 1904.

On physical examination, the man was in no apparent acute distress. He had evidence of arteriosclerotic cardiovascular disease, but the interesting finding was that of a large, sausage-shaped mass in the left lower quadrant of the abdomen. The mass felt like bowel and was tender to touch. The liver and spleen were not palpable. A diagnosis of malignancy was entertained because of the acute onset of the lower abdominal pain of three months' duration, frequent watery bowel movements containing mucus and occasionally blood, in a man of 65 years of age, whose bowel habits had been normal until the present episode, plus the 15-pound weight loss. However, one could not ignore the x-ray impression of ulcerative colitis. He was accordingly sigmoidoscoped, and as had been reported previously, a swollen, proliferative, whitish, fat-like area was noted five inches from the rectum which constricted the bowel and bled very readily. The lumen at this point had a diameter of not more than a quarter of an inch. It was impossible

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to distend this area with air insufflation. The lesion appeared to be either a degenerative malignant mass, or an infiltrating granulomatous process.

An x-ray, Figure 1, taken before admission to the hospital by M. S. on June 29, 1944, was reported as

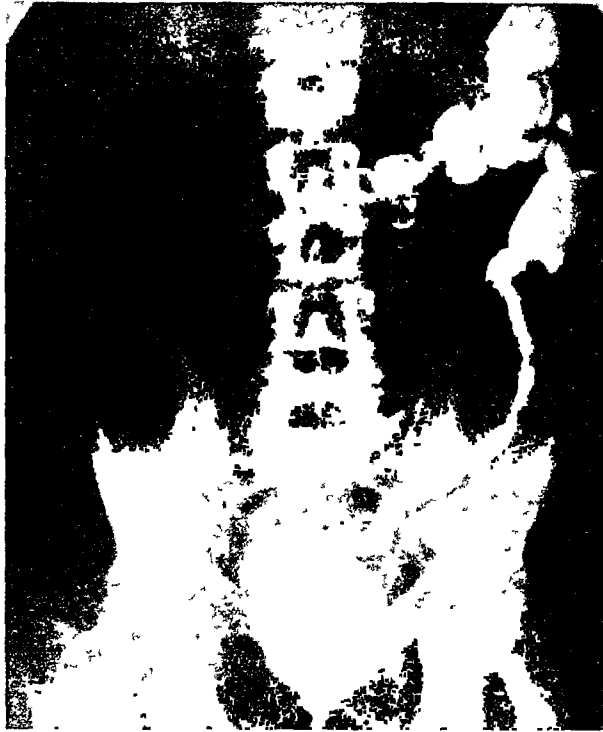


Fig 1. First barium enema study (preoperatively) June 29, 1944, showing extensive narrowing of the descending colon and sigmoid

follows: Only the distal half of the colon could be filled and that with considerable difficulty and discomfort to the patient. The picture was rather bizarre. A marked narrowing with pronounced marginal irregularity was present extending from the rectosigmoid junction to just above the mid-descending colon. The demarcation above and below was quite sharp. The rectum appeared normal and the colon proximal to the lesion although incompletely filled, seemed free of pathology. A re-examination of the colon during hospitalization on 7-28-44, presented substantially the same findings with the caliber of the involved segment appearing somewhat smaller. The roentgenologist stated that he had never seen a similar lesion in the large bowel and that in his opinion the differential diagnosis probably rested between an advanced, segmental ulcerative colitis and a granulomatous stenosing process. The extent of the lesion tended, he thought, to rule out a neoplastic lesion.

On August 7, 1944, a laparotomy was performed by B. L. The entire left side of the colon extending from the mid-transverse colon down to the mid-rectum was removed. A permanent colostomy was made from the proximal transverse colon. The specimen was sent to the laboratory and the following report was given to us by our pathologist, Dr. D. Meranze.

Macroscopic: The specimen consisted of 34 cms.

of congested, greatly thickened large bowel. A great deal of very firm, orange-yellow fat tissue is attached to its serosal surface. Embedded in the fat are several moderately enlarged greyish-pink, firm lymph nodes and a few pale yellow and pinkish-grey, ill-



Fig 2 Low power x 90 photomicrograph of intestinal mucosa showing extensive surface necrosis

delimited areas, the latter for the most part surrounding small blood vessels. A large amount of scattered subserosal hemorrhage is visible externally. The open bowel contains thin, brown, foul-smelling feces. At both ends, except for slight edema, the mucosa and wall appear essentially normal. Approximately 65 cms. from one end, for a distance of 7 cms., the mucosa is ulcerated and markedly hemorrhagic. The mucosa of the succeeding 14 cms. above this area is markedly edematous and appears slightly roughened. The wall of the bowel in these two latter areas of involvement is greatly thickened, firm, focally hemorrhagic and presents a peculiar greyish cast. Accompanying the major specimen are two pieces of congested, normal-appearing fat.

Microscopic: Extensive changes are present in the involved area, Figures 2 and 3. The most striking is a widespread, necrotizing, hemorrhagic ulceration, which in some regions has destroyed the entire thickness of the mucosal layer. Portions of the necrotic mucosa are covered with pus. In the non-ulcerated and non-necrotic area the mucosa is focally polypoid, edematous and infiltrated with varying numbers of lymphocytes, neutrophils, plasma cells and some eosinophiles. In such areas an occasional abscess is seen. Everywhere in the region of involvement, the submucosa is strikingly and greatly thickened by edema,

inflammatory cell infiltration particularly with neutrophils and lymphocytes. Foci of hemorrhage and of fibrinous exudative material are noted. Through this layer young fibrous tissue cells are plentiful, set in a background showing much peculiar, palely staining hyalin material. In both mucosa and submucosa are



Fig. 3. Low power x 90 photomicrograph of intestinal mucosa showing extensive suppurative destruction.

foci of deeply staining, fibrinoid material. The muscle layers show much edema, occasionally disruptive in character, and focal fiber necrobiosis. In the portion in contact with the serosal layer is moderate fibrous tissue infiltration and replacement. The serosal layer not in contact with the mesentery is slightly thickened by edema and connective tissue proliferation. The attached mesenteric fat shows xanthomatoid changes, much newly-formed fibrous tissue, slight lymphatic cell infiltration and hemorrhage.

An impressive feature throughout is the vascular changes notably those in the smaller vessels and particularly the veins in the mucosa, submucosa and mesenteric fat. The walls of these involved veins are thickened and appear rigidly dilated. The vessels are frequently assembled in small groups, the individual members of which are separated from each other by inflamed fibrous tissue. The muscle layer of an occasional vessel is infiltrated with lymphocytes. Some show hyalin necrosis of their walls. The lumina of some are thrombosed.

The patient was discharged after three weeks in the hospital following an uneventful postoperative convalescence. He has continued to gain weight and has enjoyed comparative good health.

On March 20, 1945, eight months after resection



Fig. 4. Small bowel enema study (postoperatively) April 27, 1945, showing normal small intestinal pattern.



Fig. 5. Same as figure 4. No extension of colonic lesion. Note dilatation of cecum and ascending colon.

of the bowel, Figure 4, the small bowel was studied by means of a small intestinal enema (Schatski¹²). The purpose of this examination was to ascertain the presence or absence of a regional ileitis. The jejunum and



Fig. 6. Small bowel enema study, May 13, 1946, showing normal intestinal pattern with no evidence of extension of the original process.

ileum were completely filled and satisfactorily visualized in about 40 minutes. The loop of the small bowel were freely mobile and presented a normal pattern. The colon was filled to the point of the colostomy. There was no leakage of the contrast medium during the 1½ hours of study. An interesting finding was the dilated cecum and proximal ascending colon which may have assumed the functions of a reservoir, similar to the rectum in the normal defecation, Figure 5.

He was x-rayed again in May, 1946, 22 months after operation. He had gained weight, felt very well, and continued to work at his trade as a jeweler. There was no evidence of recurrence of the original process.

COMMENT

The location of the pathologic process in the descending colon and sigmoid is sufficiently rare to warrant placing it on record. Follow up two years later showed that the pathologic process had been completely removed and that the large and small bowels proximal to the colostomy were normal roentgenologically, Figure 6. Its close similarity, symptomatically, to malignancy of the bowel should be borne in mind. Particularly noteworthy was the extensive area of necrotic involvement and the widespread and advanced changes noted in the blood vessels as previously described.

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Vitamins and Hormones in Nutrition — III. Infection

By

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THE FIRST report¹ of this series dealt with the synergistic action of vitamins and hormones, and the influence on vitamin absorption of such contributing factors as endocrine dyscrasia, infection, gastro-intestinal disease, reduced dietary intake, emotional upset, and trauma. The effect of hormone dyscrasia on vitamin absorption was discussed in detail in the second communication². The present report, the third in the series, is concerned with the significance of infection as an etiological factor in nutritional disturbances. Observations have been based on 200 cases, as analyzed in the original communication, in 60 per cent of which infection was the significant contributing factor, ranking second in etiological importance.

Recently, considerable data have been presented in evidence of the important role of vitamins, specifically A, C, D, and the B complex, in resistance to infection. It has been demonstrated that a relative deficiency or complete absence of the vitamin B complex from the diet will lead to deleterious effects on normal growth, gastro-intestinal function, and the nervous system, followed by increased susceptibility to certain types of infection. Unfortunately, these facts have been so exploited commercially that many physicians are hesitant to accept them, or they prescribe vitamins with grave doubt as to their efficacy. However, in view of more recent findings, this increased susceptibility to infection in the presence of vitamin deficiency has been re-emphasized, and can be regarded as a manifestation of impaired metabolic activity.

And once established, infection will interfere with

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the absorption and synthesis of vitamins. This has been demonstrated by clinical data, and corroborated by well-controlled experiments. The mechanism by which this is brought about has been clarified by recent investigations demonstrating that where there is infection the metabolic rate is increased. This induces a greater demand for essential food elements which must be provided by the reserves in body tissues. The health of tissues and organs of the body depends on the normal functioning of the individual cells of which they are composed. And each cell must play its part, not only in the metabolism of food, but in the chemical reactions concerned with the utilization of hormones and vitamins. In health a constant physiological balance of the cell chemistry is maintained and is delicately adjusted according to energy requirements. Now, infection, with its possible bacteremia and usual toxemia, interferes with the normal chemical processes in individual cell metabolism, and thus alters the absorptive capacity and nutrition in that cell. Infection, especially of the chronic type, sets up a barrier which obstructs, alters, or interferes with the orderly mechanism attending the important roles of hormones and vitamins. Under such circumstances physiological balance is bound to be upset.

As time goes on the deficiency states are being recognized quite accurately by clinicians, and therapy is directed to their correction. Surgeons, following the lead of endocrinologists and internists, realize the importance of correcting any known chemical imbalance. Not only that, but they actually anticipate the failure of cell function from the effects of infections and disease processes. As a result, the preoperative preparation and the postoperative care is carefully adapted to meet any possible imbalance. Experience, especially during the past decade in both civilian and military circles², has taught surgeons to consider their patients from this physiological point of view. In patients with infections, before considering operative procedures, the surgeon thinks in terms of sodium, potassium, chloride, and water balance. He evaluates the nutritional³ and metabolic states. Knowing that in the presence of infection there is a pathological trend in the physiology, he supplies, fortifies, substitutes or replaces the needed minerals, chemicals, food elements, vitamins or hormones. These can all be given parenterally at first if oral administration cannot be utilized. Careful physical examination, laboratory studies and clinical judgment provide the clues toward the necessary corrective or substitutive measures that should be taken.

Some ten years ago, for example, in a case of acute cholecystitis complicated by empyema of the gallbladder, the surgeon would first drain the gallbladder, and later, when the patient's condition would be more favorable, he would perform a cholecystectomy. Today, extension of the empyema would likely be checked by a course of sulfonamides, antibiotics, or a combination of both. Preoperatively the patient would likely be fortified with intravenous or parenteral saline solution, hydrolyzed proteins, plasma, whole blood, glucose, vitamin B complex, and vitamin K, in order to

anticipate disturbances of the chemical and physiological functions which might otherwise appear. This present day approach has resulted in improved surgical convalescence and end results, simply because the nutritional status is considered before operation. In this way postoperative deficiencies, with lowering of nutritional levels, can be forestalled because preventative measures thus taken protect against the disruption of the normal metabolism of essential food elements.

From this brief discussion of the mechanism of infection in nutritional disorders it is evident that the true damaging agents are the toxins of pathogenic bacteria which produce a systemic toxemia. The site, extent, and severity of the infection are significant only as diagnostic and therapeutic guides. It makes little difference where the infection is, whether it be extensive or restricted in area, acute, subacute, or chronic. The resultant toxemia interferes with or inhibits vitamin absorption and synthesis, and therefore nutritional deficiencies result. Therapy must be directed toward eradication of all infective foci, and toward restoration of individual cellular nutritional levels by proper diet and complete replacement therapy.

Replacement therapy, as employed in such cases, attempts to replace the chemical balance of hormones and vitamins, similar to the chemical balance established in preoperative treatment. By substitution therapy or replacement therapy is meant a normal, well balanced diet, plus the replacement of all metabolic factors necessary in physiological balance, that is:

1. Elementary food factors:
 - a. proteins (hydrolyzed proteins)
 - b. Carbohydrates (intravenous glucose)
 - c. Fats (lipoids of liver)
2. Minerals
3. Vitamins
4. Hormones
5. Fluid balance

complete substitution therapy must take into consideration any upset in the normal levels of these essential nutrients, and in the event of such an upset, substitution must be made for that individual factor or group of factors.

The application of these etiologic and therapeutic principles to specific cases is illustrated in the six cases selected for analysis. It will be noted that the first three cases are males, in whom the prostate gland was the primary chronic infective focus. In the search for a focus of infection, chronic foci have, perhaps, most commonly eluded recognition. The prostate has been found to be one of the chief sites of chronic infection in the male. It has been notoriously overlooked as a possible focus of infection in a great majority of cases, or, when recognized, has frequently been inadequately treated. A large group of male patients, observed by the author, had previously been treated for prostatitis. Therapy consisted chiefly of massage, and in some cases bladder irrigations had been given at the same time. These patients had been discharged as apparently cured, but subsequent examination by the author usually revealed a large boggy gland, with prostatic

smears showing only a few pus cells at first. Soon after hormone and vitamin replacement therapy had been instituted, however, large numbers of pus cells were found in subsequent smears.

The reason for this increased discharge of pus cells becomes apparent upon analysis of the factors involved. That alteration in sex hormone balance occurs at the climacteric period in both sexes has been well established. Is it not conceivable, therefore, that hormonal imbalance can be an important factor in simple hypertrophy associated with infection of the prostate gland? Moreover, it was demonstrated in the second report of this series² that endocrine dyscrasia will interfere with the synthesis and absorption of vitamins. It seems reasonable to assume, then, that establishment of the hormone vitamin balance by replacement therapy produces further drainage of pus which could not be obtained by routine genito-urinary therapy. This accounts for the discovery of further infection in a gland which had previously been considered normal.

In many of these prostatic cases further investigation may reveal other foci of infection which contribute to the chronicity of the primary focus. Among these secondary foci are abscessed teeth, subacute sinusitis, subacute hepatitis, and chronic bronchiectasis. Treatment of these secondary foci by increased drainage or surgical eradication aids materially in alleviating the primary prostatitis. Along with the direct attention to the secondary foci of infection, replacement therapy, with both vitamins and hormones, must be continuously given. Presentation of specific cases may serve to illustrate these various points.

CASE I

The first case is that of a male at the climacteric period, with tertiary syphilis, and chronic infectious hypertrophied obstructive prostatitis, which complicated an old gonorrheal postrate abscess. The patient, aged 56, complained of dysuria, nocturia, incontinence and impotence of several years' duration. Severe headaches, vertigo, blurred vision, and shoulder pain had persisted for three years. During this same period the patient had observed diminished pressure and narrowing of the urinary stream, and some dribbling. Mild constipation had occurred in the past year. The past history is rather ironical insofar as the patient had experienced sexual relations on only one occasion, at the age of 28. From this single contact he contracted both acute gonorrhea and syphilis. The gonorrhea had been treated and the infection arrested, but he was unaware of his luetic infection until the time of the present consultation, twenty-eight years later.

Physical examination revealed a thin, well developed male. The hair was dry with extensive achromotrichia. Numerous topi were present on both ear lobes. The pupils of the eyes were irregular, with Argyll Robertson reaction. The sclerae showed a slight icteric tinge, and were slightly injected. Slight circulatory nystagmus and moderate arcus senilis were observed. Ophthalmoscopic examination of the ocular fundi showed moderate arteriosclerotic changes with yellow pigmentation and exudate along the central vein bilaterally. Moderate recession of the gums was noted, as well as extensive leukoplakial changes of the buccal mucous membranes. A chain of cervical glands was palpated, and there were slight pulsations of the external jugular vein. There was depression of the manubrium sternum, with a rachitic rosary of the sternocostal junctions. Medium crepitant rales were heard at the base of the left lung after cough. Abdominal examination revealed a slightly irregular, firm, non-tender liver edge, palpable two fingers below the right costal margin. The spleen was barely palpable. Rectal examination revealed the prostate to be tremendously enlarged, hard, tender, the median sulcus not palpable. The skin was thickened and dry. Moderate hypertrophic changes had occurred in the larger joints. Reflexes were hyperactive, with ankle clonus and absent knee jerks. Laboratory

data revealed the basal metabolic rate to be somewhat depressed, and blood counts and blood chemistry within normal ranges. Fasting non protein nitrogen was 38 mg. per 100 cc. of blood. Microscopic examination of the urinary sediment revealed 30-40 pus cells per high-powered field. Routine blood Wassermann was positive, as were repeated Hinton and Kahn tests, as well as the spinal fluid.

Specific anti-syphilitic therapy was instituted, parenterally and orally. A well balanced diet of high protein and high vitamin content was prescribed. Thyroid extract was given to increase the lowered metabolic level. Androgen, in the form of methyl testosterone, and estrogen, in the form of diethylstilbestrol, were prescribed orally to help maintain a normal androgen-estrogen balance. The subclinical avitaminosis was treated orally with vitamins A, D, C, E, and a potent elixir of the vitamin B complex. Sodium chloride, ammonium chloride, calcium gluconate, potassium iodide, and molybdenum were prescribed orally to restore the mineral balance.

The purpose of parenteral therapy was threefold: to establish a hormone and vitamin balance more quickly, to insure proper absorption, of ingested food, and to detoxify the liver in order to prevent destruction of hormones by that organ. Liver extract, vitamin B complex, thiamine chloride, and vitamin C were given parenterally for the avitaminosis. Testosterone propionate was substituted parenterally for the androgen factor, and ketohydroxyestrone and alpha estradiol dipropionate for the estrogen balance. For a short time an anterior pituitary like hormone was administered subcutaneously to aid establishment of an androgen-estrogen balance through the gonadotropic factors of the anterior pituitary gland.

During the routine anti-luetic treatment, toxic reactions were encountered in the intravenous administration of neoarsphenamine or mapharsen. Invariably, irrespective of the dosage, nausea and vomiting developed, either during administration or immediately after the injection. An elixir of the whole vitamin B complex and para-aminobenzoic acid were added to the oral medications, and the whole vitamin B complex was given intravenously, following which toxic manifestations subsided. The action of para-aminobenzoic acid and the vitamin B complex as detoxifiers has been mentioned in previous communications of the author's⁴⁻⁵ and elsewhere in the literature.⁶⁻⁹

Prostatic massages were given twice a week for the first few months, then reduced to once per week. Microscopic examination of the prostatic smear after the first massage revealed 0-4 pus cells per high powered field, but at the third massage 80-200 pus cells per high powered field were seen. Prostatic smears continued to be loaded with sterile pus cells for months.

At check-up examination six months after the first consultation, the patient's general condition was greatly improved. There was improvement of the force and calibre of the urinary stream, with no further dribbling. On physical examination the hair was moist and of much better quality. Retinal vessels showed considerable dilatation, and the conjunctivae and sclerae were clear. The ear lobes were almost entirely clear of topi. The gums were firmer, and only residual leukoplakial areas remained on the buccal mucous membranes. Only a few cervical glands were palpated. Heart measurements and blood pressure were within nearly normal ranges. Heart sounds were of much better quality, regular, with decreased intensity of the murmurs. The lungs were clear. Abdominal examination revealed reduction in the size of the liver, which could now be felt one finger's breadth below the right costal margin, and the spleen was no longer palpable. The prostate was reduced to about one-fifth its original size. The skin was more moist and of better tone. There was less crepitus in the larger joints, which were more freely movable. The reflexes were less active, but pathological reflexes persisted. Blood counts and chemistry showed definite improvement. Fasting non protein nitrogen was 35 mg. per 100 cc. blood. Basal metabolic rate was $\frac{1}{4}$ per cent. Urinary sediment showed 2-5 pus cells. Prostatic smear revealed 25-50 pus cells per high-powered field.

Adherence to the therapeutic regime described has maintained the patient at fairly normal levels for the past three years, with very few subjective complaints. The blood Hinton remained positive, but the spinal fluid became negative. Prostatic massages have been continued, with gradual reduction in the number of pus cells.

A complication of diseases had occurred in this first case, which had upset the nutritional balance for many years. Symptoms became more pronounced at the climacteric period and were further enhanced by a focus of infection, the prostate gland. Eradication

of the infective focus, and establishment of hormone and vitamin balance by proper diet and complete substitution therapy resulted in an improved physiological balance, even though a positive luetic blood stream infection persisted.

CASE 2

The second case is that of a 44 year old, single, white mechanic who complained of bizarre symptoms over a four to five year period. Amongst his major complaints were listlessness, fatigue, constipation, headache, backache, mental depression, irritability, gain in weight, and loss of libido. Rapidly progressive graying of the hair had been observed over a three year period. He had just completed an eight-months' course of treatments for prostatitis by a competent urologist.

Physical examination revealed an obese male, with extensive achromotrichia, dryness of the hair and skin, and ridged thickened fingernails. The upper and lower eyelids were markedly edematous, and the sclerae were moderately injected. Ophthalmoscopic examination revealed early narrowing, tortuosity and arteriovenous nicking of the retinal vessels. There were leukoplakia of the buccal mucous membranes, atrophic changes along the tip and lateral borders of the tongue, and some sponginess of the gums. The thyroid was moderately enlarged. The heart was moderately enlarged, and the blood pressure was somewhat elevated. Numerous coarse to medium crepitant rales were heard at both lung bases. The liver was palpable just below the right costal margin. The prostate was enlarged, hard, and the median sulcus could not be palpated. Hypertrophic changes and thickening of some of the larger joints was observed, as well as coarse tremor of the extended fingers, and hyperactive reflexes. Laboratory findings were within essentially normal limits, with slight variations. The prostatic smear was loaded with sterile pus cells, with no predominating pathogenic bacteria.

A well balanced diet, of low caloric value, was recommended. Oral replacement therapy consisted of an elixir of the whole B complex, small amounts of thyroid extract, diethylstilbestrol, vitamins A, C, D, and para-aminobenzoic acid. Testosterone propionate, ketohydroxyestrone, the anterior pituitary like factor, and crude liver were administered parenterally. Prostatic massages were given once a week.

Response to therapy was prompt, with frank improvement of both subjective complaints and physical findings. After three months, major symptoms had entirely disappeared, and physical examination showed decided improvement. Weight was at a normal level. There was no further progression of the achromotrichia, the hair was moist, with improved luster. Edema of the eyelids had completely disappeared, and the retinal vessels showed some increased dilatation. Small residual leukoplakia were present on the buccal mucous membranes. Lingual papillae were more pronounced, and the gums were firmer. The thyroid was smaller. The heart was normal in size, and the blood pressure was within a normal range. There was greater expansion of the lungs, with no rales heard on auscultation. The liver was not palpable. The skin was moist, the fingernails less ridged. Reflexes were more normal. Laboratory data were entirely normal.

Mention should here be made of the fact that, at the original consultation, the patient complained of pain in the inter-phalangeal and tarsal-phalangeal joints of both great toes. A tentative diagnosis of gout was made, based on a fasting blood uric acid of 6.9 mg. per 100 cc. of blood. No specific treatment for gout was instituted, but after four months of treatment, as outlined above, pain in the great toe subsided completely. The blood uric acid taken at that time, and at intervals since, has varied between 1.2 mg. and 1.8 mg. per 100 cc. blood.

During eighteen months of persistent replacement therapy and prostatic massages, prostatic smears showed clumps and areas loaded with sterile pus cells. A secondary focus was discovered in an infected molar, following extraction of which prostatic smears gradually became negative. At the most recent examination the prostate was essentially normal in size, the median sulcus palpable, and of normal consistency. For four years, now, this patient has been maintained at normal levels, with no recurrence of symptoms. At intervals oral medication has been supplemented by short courses of parenteral therapy and prostatic massages.

This second case demonstrates clearly the end result of systemic symptoms produced by changes in cellular nutrition. These changes themselves resulted from a primary focus of infection, the prostate gland, which after previous treatment had been judged to be normal. An abscessed tooth provided a secondary focus of infection, complicating the primary focus, and both foci interfered with vitamin ab-

sorption and hormonal secretion. The therapeutic approach consisted of removal of the foci of infection, and restoration of hormone and vitamin balance by adequate balanced diet, and complete substitution therapy.

CASE 3

The role of the prostate as a focus of infection in the male climacteric is still further illustrated in the third case. A white male, aged 52, had for ten years been subject to mental depression, extreme nervousness, and crying spells, which had become worse during the past four years. He complained of headaches, palpitation, flushes, sweats, paresthesias, insomnia, partial impotence, slight constipation, and increased fatigue. He had particularly noticed increased difficulty in urination, narrowing of the stream with dribbling at the end of micturition, and nocturia six to eight times. His appetite was poor, and he had lost 20 pounds over an eleven year period.

Physical examination revealed a thin, well developed, male. The hair was sparse and dry, intermingled with achromotrichia. The scalp was dry and scaly. There was moderate edema of the eyelids; ophthalmoscopic examination of the ocular fundi revealed moderate arteriovenous nicking, calibre changes and tortuosity of the vessels, with areas of dark pigmentation along the larger vessels. The lips and mucous membranes were slightly cyanotic, with large areas of leukoplakia throughout the buccal mucous membranes; there was sponginess and recession of the gums; and atrophic lingual papillae. The thyroid was full, particularly on the right, and small cervical adenopathies could be palpated. There was moderate enlargement of the heart. Heart sounds were of good quality, with extra-auricular beats, accentuation of the first mitral sound, and the second aortic sound was greater than the second pulmonic. Blood pressure was moderately elevated to 178 systolic, 110 diastolic. The lungs were essentially negative except for a few fine crepitant rales at the bases. The abdomen was of the scaphoid type. There was marked voluntary spasm, with hyperesthesia. The liver was palpable one and a half fingers below the right costal margin. The prostate was enlarged and markedly boggy. The skin was thickened and dry, the nails thickened, the hands and feet cold. There was marked crepitus in the knee and shoulder joints. Reflexes were hyperactive. Laboratory findings were at generally low levels, but the basal metabolic rate was +22 per cent, and fasting blood sugar was 193 mg. per 100 cc. of blood. The urine showed 2 per cent sugar. Prostatic smear showed 6-8 pus cells per high powered field.

The patient was placed on a high vitamin and caloric diet, low in carbohydrate content. Complete substitution therapy was instituted, consisting of an elixir of the whole B complex, vitamins A, C, D, and diethylstilbestrol, all orally administered. A course of thiouracil was given over a five month period, the dosage varying from 100 mg. two times a day to 100 mg. four times a day. Parenteral therapy consisted of testosterone propionate, ketohydroxyestrone, alpha estradiol dipropionate, vitamin B complex, liver extract, and protamine zinc insulin. Prostatic massages were given once a week.

At check-up examination six weeks later his general condition showed considerable improvement with subsidence of some of the subjective complaints, and with complete disappearance of others. There was improvement in the force and calibre of the urinary stream, no further evidence of dribbling, and nocturia only once. He had gained 3¼ pounds in weight. The hair and scalp were comparatively moist. Edema of the eyelids had completely subsided, and on examination of the ocular fundi the vessels were more dilated, with no hemorrhage or exudate. Lips and mucous membranes were of good color, and the leukoplakia were diminished. The gums were firmer, and the lingual papillae were more pronounced. The thyroid was smaller, and only a few tiny cervical adenopathies could be palpated. Heart measurements showed a definite decrease in size, the sounds were of much better quality, regular, with less accentuation of the first mitral sound. There was considerable reduction in blood pressure, 142 systolic, 84 diastolic, as compared with the original level of 178 systolic, 110 diastolic. The lungs were entirely clear. Abdominal examination revealed less voluntary spasm and hyperesthesia. The liver was reduced in size, barely palpable at the right costal margin. The prostate was somewhat decreased in size, the right lobe was more normal, with some bogginess remaining in both lobes. The skin was quite moist and of good tone, the nails firmer, the hands and feet warmer. The joints were more freely movable, with less crepitus. Reflexes were more normal. Laboratory findings in general were at high normal levels, but the fasting blood sugar was still

high at 160 mg. per 100 cc. of blood, and the basal metabolic rate was +18 per cent. The urine showed but 0.5 per cent sugar.

After six months of therapy, check-up examination revealed even greater improvement. The patient had gained a total of 10 pounds in weight. The prostate was essentially normal, with smears showing no more than 1-3 pus cells per high powered field. Laboratory data at this time revealed a normal blood and urine. The fasting blood sugar was 110 mg. per 100 cc. of blood. The basal metabolic rate was +8 per cent, thiouracil having been stopped one month previously.

A typical male climacteric syndrome with resultant nutritional changes is illustrated in this case. Parenteral and oral substitution therapy partially re-established the vitamin hormone balance, but until the prostatic focus had been cleared, complete physiological balance could not be established. The patient's general condition has been maintained at nearly normal levels over a three year period.

The three cases just described exemplify a frequently encountered primary focus of infection in the male. An infected prostate which has been present for many years, can lead to a nutritional imbalance. The following three cases, all women, illustrate unusual instances of infection, any one of which can act as a primary focus. The fifth case represents not only an unusual focus, but an uncommonly encountered organism, one which should now be searched for more frequently with the return of our war veterans from the Pacific theatre. The sixth case illustrates a complicated deficiency state resulting from multiple foci of infection.

CASE 4

The nasal sinuses were finally revealed to be the chief focus of infection in this fourth case to be presented. A 26 year old, married female complained chiefly of obesity, with a weight gain of 46 pounds over a five year period, 20 pounds having been added during the previous year. Associated with the gain in weight were the usual complaints of fatigue, anorexia, headache, backache, constipation, and frequent excessive perspiration. Her past history revealed frequent colds, with sore throat. She had noticed dryness of the hair and skin, and brittleness of the fingernails. The menstrual cycle was normal in interval and duration, with dysmenorrhea the first day. The patient was sterile. The appendix and a polycystic left ovary had been removed at age 20.

Physical examination revealed an obese, well developed female. The hair was dry and lusterless, the scalp scaly. There was slight edema of the eyelids, and pallor of the conjunctivae. The nasal septum was slightly deviated to the right. Buccal mucous membranes were somewhat pale, with leukoplakia distributed throughout. The tongue was somewhat coated, protruded in the midline, with a coarse tremor; lingual papillae were atrophic. There was hypertrophy and erythema of the lymphoid tissue of the pharynx. Teeth showed evidence of decalcification, and the gums were somewhat spongy. The thyroid gland was barely palpable, with a few small cervical adenopathies. The heart was moderately enlarged, the sounds of good quality, with sinus arrhythmia. Slight dulness at the left base, broncho-vesicular breathing, and occasional fine crepitant rales were observed at the base of the left lung. Abdominal examination was negative except for a well healed postoperative scar. Pelvic examination revealed small areas of glistening, atrophic vaginal mucosa, first degree retroversion of the fundus, an ulcerated erosion of the cervix, and thickening in the left vault probably due to postoperative adhesions. The skin was dry and somewhat thickened. Fingernails were brittle and ridged, and there was moderate tremor of the extended fingers. Other findings were essentially normal, with laboratory data within normal ranges. The basal metabolic rate was -14 per cent.

The patient was placed on a well balanced diet, of low caloric content, and small amounts of thyroid were administered daily. Under this regime her condition improved somewhat, with gradual reduction in weight to normal levels. The severity and frequency of the colds persisted, however, proving intractable to therapy. Change to a warmer climate during the winter months afforded only temporary relief. The patient went along in this condition for about eighteen months. At this time she was greatly concerned about her

sterility, and at her request a plastic operation was performed on the right fallopian tube, and salpingostomy on the left tube. In the course of the next year a severe *Trichomonas vaginalis* infection developed and was treated successfully. At check-up examinations during this period signs of avitaminosis and endocrine dyscrasia had become more evident, there had been further weight loss, and laboratory data were considerable below normal standards.

A well balanced, high caloric diet was prescribed, and parenteral substitution therapy was administered, consisting of ketohydroxyestrone, corpus luteum hormone, anterior pituitary like hormone, liver, and the vitamin B complex, in potent dosage. Under this regime, and following clearance of the pelvic infection, the patient's general condition improved, but upper respiratory infections still persisted. At this point the patient contracted a tracheo-bronchial infection, complicated by pleurisy, and right nasal antrum infection. Examination by a competent nose and throat surgeon, his findings corroborated by x-ray examination, revealed a severe pansinusitis with an abscess in the right antrum. The presence of an abscess in the antrum, along with marked thickening of the antral mucous membranes, indicated clearly that the nasal sinuses had long been the hidden primary focus of infection, even though a number of examinations and x-rays done previously had been reported negative.

Daily irrigations, with other appropriate treatments, were given by the laryngologist to clear the infected sinuses. The patient continued on a high-caloric diet, and a regime of complete substitution therapy with vitamins and hormones, consisting chiefly of thyroid extract and the whole B complex orally, and ketohydroxyestrone, corpus luteum hormone, anterior pituitary like hormone, and liver extract parenterally administered. At check-up examination six months following institution of this regime the patient volunteered that she felt better than she had in years. She had regained 10 1/4 pounds of the weight loss which had occurred during the period of infection. She had been entirely free from colds during this period, and her subjective complaints had subsided. Physical examination at this time revealed definite improvement. Her hair was moist and of good luster. There was no edema of the eyelids, and the conjunctivae were of normal color. The sinuses were clear on transillumination. The buccal mucous membranes were of good color, with only slight residual leukoplakia. Atrophic areas of the tongue had filled in almost completely, and the throat was more normal. Cervical adenopathies had disappeared. Heart measurements were within normal limits, the sounds of good quality, and regular. Blood pressure was within normal ranges. The lungs were entirely negative. Pelvic examination revealed a normal vaginal mucosa. The cervix was entirely healed. The skin was moist and of better tone. The fingernails were firmer, with disappearance of ridging. There was no tremor of the extended fingers. Laboratory data showed definite improvement, with normal blood counts, and differential smear. Blood chemistry was within normal levels. Basal metabolic rate was -2 per cent.

Here we have an example of persistent nutritional changes which at first improved only slightly under hormone and vitamin substitution therapy. Until the hidden primary focus of infection, the nasal sinuses, had been cleared, general physiological balance could not be established. But, with eradication of the infective focus, substitution therapy with vitamins and hormones was effective in restoring the body to a normal nutritional condition, which has been maintained for four years. The patient during this period has been free from symptoms, and has had only a rare, mild cold.

CASE 5

The fifth patient is an unmarried female, aged 26, whose chief complaint was paresthesias of the upper extremities of six weeks' duration. Three months previously the patient first became conscious of pressure low in the right lower quadrant, which radiated through to the back and spine, and was aggravated by bending the head forward. Paresthesias of the left upper extremity were first noticed six weeks prior to consultation. Two weeks later the patient noticed paresthesias of the right upper extremity. Muscular weakness then developed in both hands, for she found it increasingly difficult to dress herself. This was followed by paresthesias and coldness of the left foot, along with general paresthesias throughout the left side of the body. She noticed increasing fatigue, with sleepiness during the day. Her hearing had become less acute. Her appetite remained normal, constipation became more marked. Her weight had remained constant for the past two years, although a year previously

she had lost 15 pounds by voluntary dieting. She complained of intermittent headaches, soreness and bleeding of the gums, precordial pressure, and slight hacking cough. Menstrual flow had decreased in duration and volume over the past few months. She had developed headaches the last two days of the period during the same interval. One week before consultation the patient observed edema of the entire left arm which was tender to palpation. The past history was irrelevant except for a fractured nose sustained during an automobile accident four months previous to consultation. As a child, at age 4 to 5, the patient had been kept on a sugar-free diet because of a question of diabetes mellitus. As far as could be determined a glycosuria had been found, but at no time had hyperglycemia been looked for. Achromotrichia had developed over a period of ten years, but became more pronounced during the past year.

Physical examination revealed a thin, well developed female, showing marked evidence of avitaminosis: dry lusterless hair, extensive achromotrichia, scaly scalp, dry thickened skin, atrophic lingual papillae, extensive leukoplakia of the buccal mucous membranes. There was edema and redness of the eyelids. Ophthalmoscopic examination showed definite haziness of the nasal side of the optic disc bilaterally. The gums were spongy, hypertrophied, and bled on slight pressure. There was fine tremor of the tongue. The pharynx showed follicular hypertrophy. The neck was somewhat rigid with limited motion. The thyroid gland was moderately enlarged, and a few small cervical glands could be palpated. The heart was slightly enlarged, the sounds of good quality, the first mitral sound was somewhat accentuated, with a grade I systolic murmur at the base. Abdominal examination revealed a slightly tender, smooth liver, palpable one finger below the right costal margin. The spleen was barely palpable at the left costal margin. Pelvic examination was essentially negative except for slight enlargement of the right ovary with questionable cystic changes. The skin was somewhat dry and thickened. The extremities were cold, particularly on the left side, with some mottling and redness of the feet. Dorsalis pedis and posterior tibial vessels were feebly palpable on the right, entirely absent on the left. The muscles of the left hand and forearm were slightly atrophied. The nails were soft, yet brittle. There was coarse tremor of the extremities, more pronounced on the left. On the left side the knee and ankle reflexes were hyperactive, and the Babinski reflex was positive. Abdominal reflexes were absent. No Kernig, Oppenheim, or Gordon reflexes were observed. Biceps and triceps reactions were two plus on the left, and the muscular power was slightly diminished on the left side. Past pointing was found bilaterally. Laboratory findings were all at low normal, or subnormal levels, but the white cell count was elevated to 10,400. Basal metabolic rate was -5 per cent. Hinton test was negative.

One week later the patient was hospitalized, where a regime of substitution therapy was strictly followed. Oral medications included thyroid extract, the whole vitamin B complex, para-aminobenzoic acid, and vitamins A, C, D, with calcium and minerals. Parenteral therapy consisted of thiamine chloride, pyridoxine hydrochloride, liver extract, alpha estradiol dipropionate, and the whole B complex. Complete laboratory studies were repeated at regular intervals. On the third day of hospitalization there was a moderate drop in the blood counts; a lumbar puncture revealed increased initial pressure, increased pressure with left jugular collapse; spinal fluid examination showed a lymphocytic count of 20, an increase of total proteins, a negative Wassermann and goldsol reaction. After neurological consultation a provisional diagnosis of mild virus meningitis was made. Sulfadiazine was administered, and the patient's condition improved somewhat under continued therapy.

In the sixth week of hospitalization the differential smear showed 16 per cent monocytes, suggestive of agranulocytic angina, or infectious mononucleosis. At about the same time the temperature began to assume a picket fence variation with a three day cycle, that is, three days elevated, three days flat. The temperature chart became suspicious of estivo-autumnal type of malaria, although on differential smear red cells showed no plasmodium malaria. Agglutination tests for typhoid, para-typhoid, and undulant fever were negative. A therapeutic quinine test was undertaken at this time, following which the temperature subsided and finally remained normal. Despite the absence of the plasmodium bodies in the blood smears, the therapeutic response to quinine prompted a search for other possible sites which might harbor the organism. The enlarged, tender liver was not consistent with the tentative diagnosis of virus meningitis. Gallbladder drainage was performed, and the bile on both microscopic

examination and bacteriological culture revealed the plasmodium malaria. This finding substantiated a final diagnosis of chronic malaria. Quinine therapy was continued, plus gallbladder drainage, and substitution therapy was continued. Under this regime the entire picture cleared, with complete subsidence of the neurological symptoms.

Oral and parenteral substitution therapy was continued after the patient's discharge from the hospital, the regime being essentially the same as outlined at the beginning of treatment, and a well balanced, high caloric diet was prescribed. With the clearance of the infective focus, definite gradual improvement was first observed, and then a rapid return to normal health. Evidence of her restored physiological balance is provided by the fact that three months after her discharge from the hospital she contracted a mild virus pneumonia, the course of which was uneventful. Convalescence was rapid, with no impairment of physiological levels, no return of earlier symptoms, nor sequelae of any kind.

For three years this patient has been maintained at completely normal levels, chiefly on oral medications, but with some short courses of parenteral therapy. There has been no return of symptoms. At her last check-up examination she had gained 8 pounds in weight, and her general condition was remarkably improved. Her hair had a normal sheen and luster, with a decrease in the achromotrichia. There was no redness of the eyelids, and only slight edema remained. Ophthalmoscopic examination was negative. The lips and mucous membranes were markedly improved, with only a few small areas of residual leukoplakia. The gums were firm, the lingual papillae pronounced, and there was no tremor of the tongue. There was normal motion of the neck, the thyroid was normal in size. Heart measurements were within normal limits, the sounds of good quality, the rhythm regular. Blood pressure was at a normal level. Abdominal examination was essentially negative with the liver and spleen no longer palpable. On pelvic examination the right ovary appeared to be normal in size. The skin was moist and of good tone, the nails firm. Extremities were warm. Dorsalis pedis and posterior tibial vessels were palpable bilaterally. There was no tremor of the extended fingers. The reflexes were slightly diminished in the upper extremities, normal in the lower. Laboratory findings were all at normal levels, basal metabolic rate was +2 per cent.

CASE 6

The sixth case presents one of the most pronounced nutritional deficiencies in our group, complicated by several foci of infection, a marked endocrine dyscrasia, chronic gastro-intestinal disease, reduced dietary intake, emotional upset, and trauma. Classification of this case is difficult, since every etiological factor mentioned in the original communication is included but infection seems to be the principal individual factor.

The patient was a 55 year old, white, married, business woman, who complained of ill health of more than fifteen years' duration, with such symptoms as extreme fatigue, headaches, colitis, weakness, nausea, vertigo, palpitation, sweats, anorexia, dysuria, insomnia, and loss of weight. She was first seen in consultation in 1942. Fifteen years before, following a "gum infection," the patient had developed osteomyelitis of the mandible, because of which she was hospitalized for eight months. During this period surgical intervention was required on seven different occasions. Following one operative procedure, apparently in the post-anesthetic stage, she sustained a fracture of the mandible. Other complications arose when she contracted spinal meningitis of a mixed streptococcus-pneumococcus type. Later during the eight months' hospitalization she also developed mucous colitis, acute cholecystitis, acute hepatitis, and broncho-pneumonia. Loss in weight amounted to some 60 pounds.

Here we have infection, faulty dietary intake, and trauma as obvious etiological agents. Endocrine dyscrasia was a further etiological factor as disclosed by the following menstrual history. The patient at that time was 40 years old. Catamenia had become somewhat irregular, with varying degrees of dysmenorrhea. Menstrual flow had increased, lasting seven to ten days, although her normal period of flowing had been only three or four days. Persistent flushes, headaches, pruritus vulvae, mental depression, and palpitation had become increasingly pronounced over the past ten years. Thus endocrine dyscrasia of the thyro-ovarian type, complicated the case still further.

Emotional disturbance also entered into the etiological picture as can be seen in the occupational history. The patient had been engaged in many business ventures, among them conducting a small chain of hotels. The responsibility involved in this enterprise cre-

ated such severe mental strain that it added to her physical difficulties.

During the fourteen years between her hospitalization and the present consultation, the patient had felt poorly, and most of her earlier subjective complaints had persisted. For the three years directly prior to consultation, fatigue, weakness, headache, vertigo, joint pain, anorexia, abdominal distention, extreme constipation alternating with attacks of mucous colitis and insomnia had become pronounced. Extreme debility, with marked hypochromic anemia, followed the slightest infection. According to the patient she had received massive doses of iron by mouth, as well as parenteral injections of iron, arsenic, liver, and foreign protein, without correcting the anemia.

Physical examination revealed a thin, pale, hyperactive individual, with dry thickened skin, and lusterless, brittle hair. Pronounced edema of the upper and lower eyelids was seen, and considerable darkening of the skin peri-ocularly. The conjunctivae were pale and the sclerae were moderately injected. Ophthalmoscopic examination of the ocular fundi revealed slight irregularity of the discs on the nasal side, marked vascular tortuosity, arteriovenous nicking, and calibre changes of the vessels, with areas of light brown pigmentation throughout. The nasal septum was slightly deviated to the left, and the inferior turbinates were somewhat hypertrophied. Areas of leukoplakia were scattered throughout the buccal mucous membranes, and some areas were seen on the hard palate. There were marked atrophic changes of the papillae on the dorsum and lateral border of the tongue. The pharynx was red, edematous, with some follicular hypertrophy. The thyroid was full, and small cervical adenopathies were palpated. Partial ankylosis of the right temporo-mandibular joint was found. The heart was enlarged and the sounds were of fair quality, but somewhat distant. There was slight accentuation of the first mitral sound, and the second pulmonic sound was greater than the second aortic. Blood pressure was low. Slight dulness and somewhat diminished tactile and vocal fremitus was found at the base of the left lung, with numerous medium crepitant rales. The abdomen was markedly distended, with superficial tenderness. The liver was palpable three fingers below the right costal margin, smooth and slightly tender. On deep palpation there was spasm and moderate tenderness over the gallbladder. There was some tenderness along the course of the ascending and descending colon. Slight spasm with tenderness was evident at the left costo-vertebral angle. On auscultation peristalsis appeared to be markedly decreased. Pelvic examination revealed atrophic vaginal mucous membranes, with glistening areas. The uterus was of the senile type, the adnexa normal. Examination of the joints revealed crepitus in the larger joints, with pronounced Heberden's nodes at the interphalangeal joints of the fingers. The skin was thickened and dry, and there were numerous pigmented nevi throughout the body, with a large number of keratotic dark brown papillae scattered over the upper and mid abdomen. The extremities were cold, with beginning hallux valgus, and some clubbing of the fingers. There was coarse tremor of the extended fingers, and reflexes were hyperactive throughout, except for the knee jerks and abdominal reflexes which were somewhat diminished. Laboratory data were at low normal levels. Basal metabolic rate was -6 per cent.

In view of the fact that obvious nutritional deficiency had existed for fifteen years, frequent parenteral therapy was essential. This consisted of massive doses of the whole vitamin B complex, thiamine chloride, pyridoxine hydrochloride, amino acids, crude liver extracts, adrenal cortex hormone, insulin, and intravenous glucose. Small doses of endocrines were administered parenterally, namely, alpha estradiol dipropionate, ketohydroxyestrone, anterior pituitary like hormone, and deproteinized pancreatic extract. Injections were given daily for a short time, then on alternating days over a two month period, and then twice a week. Oral medication was also indicated, consisting of thyroid extract, alpha estradiol, vitamins A, C, D, E, the whole B complex, hydrolysed proteins, banana powder, decholic acid, and mineral oil.

After the first month of therapy, gallbladder drainage was done, with washings of essence of caroid and 50 per cent magnesium sulphate. Thickened, viscous mucus, black-green bile, and crystals of black bile salts were obtained. Microscopic analysis showed large numbers of mixed bacteria. Two weeks later duodenal drainage was repeated. 20 cc. of 10 per cent solution of the sodium salt of dehydrocholic acid was slowly administered intravenously, followed by 50 cc. of 50 per cent glucose, and the whole B complex with ascorbic acid 500 mg. An injection of regular insulin, Units XXX,

was given subcutaneously. The patient's response was dramatic. Before the drainage the liver was tender, its edge could be palpated 4 fingers above the pelvic brim, but within twenty minutes after the drainage an actual decrease in size and tenderness could be noted, the edge being palpable at a level 2 fingers below the right costal margin.

The patient improved rapidly following this procedure. Gastric distress, distention, and nausea subsided. Attacks of mucous colitis became less frequent. Four weeks later a second duodenal drainage and treatment was done, similar to the one just described, except that 10 cc. of a 20 per cent solution of decholic acid was used. Following this treatment the patient had no further major attacks of colitis.

After six months of treatment the patient showed a marked systemic improvement, with complete absence of her major symptoms. In the first two months of therapy she had gained 10 pounds in weight. For the first time in fifteen years her blood counts and chemistry attained normal levels, and have been maintained at these levels up to the present time. Over the past eighteen months two major infections were overcome with the aid of penicillin, with comparatively little change in the blood picture and relatively little debility. The last infection was a severe nasal pan-sinusitis which responded well to large doses of penicillin, and daily lavage of the sinuses. It is the author's belief that the sinuses were the hidden focus of infection in this case.

At her last check-up examination physical findings corresponded with the subjective improvement. The hair was moist and of good luster, the scalp clean. Edema of the eyelids had completely subsided, and fundal examination revealed no increase in arteriosclerotic changes of the vessels. Nasal turbinates were more normal. Lingual papillae were more pronounced, a few atrophic areas still remaining at the tip and lateral borders of the tongue. The thyroid was smaller, and only a few small cervical glands were palpated. Heart measurements were nearly within normal range. Heart sounds were of good quality, regular, the first mitral sound was only slightly accentuated, and the second pulmonic and second aortic sounds were equal. Blood pressure was at a more normal level. The abdomen was soft, with no tenderness nor distention. The liver edge was barely palpable at the right costal margin. Peristalsis was normal on auscultation. Pelvic examination revealed more normal vaginal mucosa. The joints were more freely movable, with somewhat less crepitus in the larger joints. The skin was moist and of good tone. There was a reduction in the number of verrucous papillae on the abdomen, and a marked lightening of the brown pigmented nevi. Extremities were warm, dorsalis pedis and posterior tibial vessels were forceful on palpation. There was no edema of the extremities, and no tremor of the extended fingers. Reflexes were essentially normal. Laboratory data showed definite improvement. Basal metabolic rate was +2 per cent.

Of particular significance in this case is the fact that a persistent mucous colitis of thirteen years' duration was entirely cleared by the prescribed therapy, with no recurrence over a two year period. This fact further emphasizes the relationship between endocrine dyscrasia, avitaminosis, infective foci, and hypoproteinemia.

The patient is now maintained on oral medication, with parenteral injections once or twice per week. At intervals injections have been omitted for six to twelve weeks at a time, but oral therapy has been uninterrupted. Recognition of recurrent mild symptoms has at times prompted the patient to voluntarily request extra "booster" injections. Recently, a whole liver factor*, with added factors of the vitamin B complex, and inclusive of the lipoids of liver, has been added to the oral medications. This new factor is regarded as an important therapeutic addition in this and similar cases, which may decrease the necessity for prolonged parenteral therapy. It has been employed for too short a time to draw any definite conclusions as yet, but clinical evidence obtained over a four-month period is most encouraging. A detailed report on this new whole liver factor will be sub-

*Material supplied through the courtesy of Rawl Chemists, Brooklyn, New York. Trade name "Rawl Whole Liver Vitamin B Complex Capsules," each capsule containing: Whole liver substance (1-3) 500.0 mgs. containing all the lipid and water soluble B complex factors as found in whole liver; thiamine hydrochloride 1.0 mg.; riboflavin 2.0 mgs.; niacinamide 5.0 mgs.; choline chloride 12.0 mgs.; pyridoxine hydrochloride 0.2 mgs.; calcium pantothenate 0.2 mg.; biotin 600.0 mmcg.

mitted later, when more clinical data are available, and based on a longer period of observation.

On the basis of the six cases just discussed in detail, the role of infection in the production of nutritional disorders, by disruption of the synergistic action of vitamins and hormones becomes apparent. Further substantiation is provided in the fact that infection constituted the chief etiological factor in 60 per cent of the original series of 200 cases. In every case previous therapy had been of little benefit until active foci of infection were cleared, and vitamin and hormone deficiencies were corrected by restoration of individual cellular nutritional levels through proper diet and complete replacement therapy. Not until all of these factors had been considered, corrected, and adjusted, could subsidence of subjective complaints, with corresponding improvement in physical findings and laboratory data be obtained.

Maintenance of normal levels over a long period of time is equally important. In order to accomplish this, no single therapeutic factor can be neglected. For example, as illustrated in the sixth case, in the presence of gastro-intestinal disorder, absorption of ingested food or oral medication was embarrassed. Therefore, parenteral substitution therapy was administered during that period in order to restore and maintain nutritional levels. After clearing up the gastro-intestinal upset, oral medication sufficed. The same is true in the majority of cases, that oral medication will be adequate,

for limited periods, once a precipitating factor like infection has been eradicated, and normal physiological balance is achieved. But it is imperative in all cases that constant observation be maintained in order to detect those periods of mild regression, when a short course of parenteral therapy may be required to re-establish and preserve chemical balance. Only by continued vigilance and observation can physiological balance be achieved and maintained.

CONCLUSIONS

1. Infection constituted the chief etiological factor in 60 per cent of a series of 200 cases of nutritional disorders.
2. Six representative cases have been selected from the original series for detailed discussion and analysis.
3. The prostate has been demonstrated to be a common focus of infection in the male, but one which is frequently overlooked, or inadequately treated.
4. Therapy must be directed toward eradication of all foci of infection, and toward restoration of vitamin and hormone deficiencies by complete substitution therapy, as herein defined.
5. Proper diet and substitution therapy, along with eradication of infection, in these cases attempts to restore to normal the chemical processes which have been disrupted. By so doing, the synergistic activity of vitamins and hormones can be re-established and normal nutrition and health maintained.

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Diagnosis of the Diseases of the Pancreas

By

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DISEASES of the pancreas and of the pancreatic duct are analogous to diseases of the liver and the bile-duct.

In case of disintegration of the liver or the pancreas, those substances that are produced or changed in their cells are liberated and enter the blood vessels in excessive amounts. In acute yellow atrophy, bilirubin and the aminoacids are augmented in the blood and urine. In acute hemorrhagic pancreatitis, amylase and sugar are similarly increased.

In case of stricture or obstruction of the ducts, the results are quite the same. More striking under those circumstances, however, is the defective digestion of foods, due to the lack of bile or steapsin and trypsin, respectively.

If the bile duct is obstructed, the coloring of the feces, and resorption of the fats and urobilin in the urine are reduced, whereas in the pancreatic duct obstruction, fat splitting and muscle fiber digestion are lessened. As both ducts generally have a common opening into the papilla Vateri, emptying of each one may be hindered.

The increase of amylase and sugar in the blood and urine after pancreatic duct obstruction is not permanent. Therefore, laboratory tests have to be repeated, if results are negative. The reasons for this fluctuation are not quite evident.

A small amount of diastase is found under normal conditions in blood and urine.¹ After experimental ligation of the pancreatic duct, the amylase in the urine and blood is highly increased for some time. We observed² the quantity of diastase in the blood of the pancreatico-duodenal vein to be not higher than in other veins. Therefore, we assumed that the diastatic ferment leaves the pancreas by way of the lymph vessels.

The intermittent increase after ligation or obstruction of the duct may be due to changes in the accumulation or to destruction of ferment-producing cells with subsequent increased absorption from time to time.

What is the reason of the temporary hyperglycemia and glycosuria? Normally, insulin flows through the pancreatico-duodenal vein into the general circulation: When blood from this vein was taken from a dog, previously fed with carbohydrates, and infused into another depancreatized diabetic dog, we observed³ the disappearance of glycosuria for several hours.

Ligation of the pancreatic duct has no significant influence on the islets of Langerhans. Minor hyperglycemia following the above procedure, or an obstruction of the duct, may, therefore, be due to a damage of insulin caused by the blocked and overflowing pancreatic ferments.

In disintegration of the pancreas, however, as in

acute hemorrhagic pancreatitis, the destruction of the pancreatic tissue includes the islets of Langerhans. Consequently, hyperglycemia and glycosuria in that case are symptoms of a temporary diabetes.

In case of obstruction, the decrease or lack of pancreatic ferments can be determined by means of a duodenal tube and examination of the aspirated duodenal content. The results are more satisfactory after stimulation of the pancreatic secretion by previous administration of secretin. In this way, Diamond and Siegel⁴⁻⁵ obtained good results.

It is easier, however, to observe the feces after the intake of foods, which are digested exclusively by the pancreatic ferments. In the early stages of the disease, or if the patient does not partake enough of those particular foods, the deficiency may well be overlooked.

Therefore, a test was suggested by the author,⁶⁻⁷ with a sufficient amount of a fat which is digested only by pancreatic steapsin and which does not become rancid. Such a fat is Palmin. Other hydrated fats, however, may be used and may be found adaptable, such as "Crisco".

Faulty secretion or no secretion of steapsin results in lack of fat splitting in the stomach, together with coinshaped, white pieces of undigested fat in the stools.

Simultaneously, trypsin can be checked by the intake of a sufficient amount of dark meat. The undigested meat fibers reappear in the stools as red dots and can be detected even macroscopically.

The procedure is the following:

1st Day: For lunch and dinner about a quarter of a pound of chopped dark beef, and a serving of mashed potatoes. Add to the mashed potatoes 1-2 heaping tablespoonful of Palmin, or of another hydrated fat, stirring it, while the potatoes are still hot. Only fats may be used which are exclusively split by the pancreatic ferments and do not get rancid. From this point on, all stools should be kept for examination.

2nd Day: In the morning, on an empty stomach, a level teaspoonful of sodium bicarbonate in 200 cc. of water. Half an hour later, a breakfast consisting of tea with sugar, and a serving of mashed potatoes prepared with the fat as described above. After 2½ or 3 hours the stomach content is aspirated and examined in the following way:

Reagents:

1. Benzine purified USP 90 cc
Benzene ad 100 cc
2. Cuprum aceticum 3 gram
Aqua. dest. add 100 cc

A part of the aspirated stomach content is shaken in

a test tube, with equal parts of Reagent 1. The upper portion is poured into another test tube. Equal parts of Reagent 2 are added and shaken. If the upper portion of the liquid remains colorless, pancreatic juice is absent. (Positive Reaction.) Under normal conditions, a green coloring of the upper portion of the liquid appears.

In rare cases the test may show no abnormality, in spite of the fact that the disease is present. For instance, normal pancreatic secretion was once observed in carcinoma of the head, because the pancreatic duct was not compressed entirely by the surrounding tumor. In another instance of cancer of the head, a small abscess developed in the obstructed pancreatic duct, and penetrated into the duodenum, permitting a normal outflow of pancreatic juice.

the left diaphragm is immobile.

The most typical abnormalities which may be observed in chronic cases are the displacement and other abnormalities of the pylorus, bulb or stomach; a wider arc of the duodenum; changes around the papilla Vateri; stasis in the descending duodenum; and a highly enlarged gallbladder of normal shape (Courvoisier) in patients with jaundice.

If the islets of Langerhans alone are affected and diabetes results, it may happen that a younger patient, unaware of being diabetic, suddenly shows symptoms of coma, which may be confused with an acute hemorrhagic pancreatitis. Excruciating pain preceding coma, described by us as "pancrealgia"¹², may be difficult to differentiate at first from acute hemorrhagic pancreatitis or surgical abdomen, especially if the urine

DIAGNOSTIC TABLE OF THE COMMON
PANCREATIC DISEASES*

	Increased Diastase	Increased Sugar	Author's Test	Occult Blood	Icterus	Ascites	Roentgen Examination
1. Acute hemorrhagic pancreatitis -----	†	†					† Flat Film
2. Cysts and pseudo-cysts -----	(†)	(†)					†
3. Obstruction of the duct -----							
a. Cancer of the head -----	†	†	†	†**	†***	(†)	†
b. Cancer or abscess of the tail -----	(†)	(†)					†
c. Cancer of the papilla Vateri -----	†	†	†	†	†		†
d. Gallstones in the papilla Vateri -----	†	†	†		†		†
e. Stones in the pancreatic duct -----	(†)	(†)	(†)				†
f. Portal lymph glands (Ca, Tb., Hodgkin) -----	(†)	(†)	(†)		†	†	
4. Celiac Disease of infants -----	Fatty stools. Other examinations difficult to perform.						

*† Frequently positive. (†) Not so frequently positive.

**If penetrating into the duodenum.

***Later.

A higher nitrogen content of the feces. "Azotorrhea" is inconclusive. The fecal nitrogen is not derived from the food alone. The characteristic symptom of reduced trypsin is the insufficient digestion of meat fibers. For that reason we suggested the expression of "Kreatorrhea" instead of "Azotorrhea".

The stools after such a diet are massive and soft, but not fluid. On the contrary, we observed a lower water content than in normal stools. This may be due to the increase of fat and muscle fibers, which in turn do not absorb as much water as normal food residues do.

Another very important aid in the diagnosis of diseases of the pancreas is the roentgenological examination. As has been summarized recently^{8,9-10}. Even in cases where it is impossible to administer a barium meal, we have seen the enlarged pancreas by means of a flat film¹¹. In cases of acute hemorrhagic pancreatitis, a flat film can still be taken without difficulty. Often

is not available for examination. Nevertheless, in the beginning, or within a short time, many a symptom may appear, which clarifies the coma. Besides other well known symptoms, the presence of soft eye bulbs and extremely low blood pressure¹³ have been observed by us as regular early symptoms.

SUMMARY

Diseases of the pancreas, such as acute hemorrhagic necrosis and stricture or obstruction of the pancreatic duct, or of the papilla Vateri, have some analogy with acute yellow atrophy of the liver and obstruction of the common bile duct, respectively.

Determination of amylase and sugar in the urine and eventually in the blood, examination of the gastric content and the feces by the method described, are recommended; roentgenological examination by a flat film or after a barium meal intake are important.

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Pathogenesis of Acute Infectious Hepatitis

By

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THE DISEASE which has come to be known as "acute infectious hepatitis" has been variously called "catarrhal jaundice," "epidemic hepatitis," etc. Present use of the term "acute infectious hepatitis" stems from the more accurate knowledge of the histopathology of the disease accumulated recently in conjunction with the development of the technique of liver biopsy.^{1,2} In describing the clinical aspects of acute infectious hepatitis authors stress the effects of the disease which pertain to the liver and therefore assume that it is primarily an affection of the liver; the importance of concomitant pathologic changes in other organs is usually subordinated.

In studying the symptomatology and laboratory data of 53 soldiers with acute infectious hepatitis in an overseas hospital, it seemed that we were dealing with a disease which was more generalized.

Because the liver is the cardinal organ involved in this illness, the tendency has been to focus attention on the findings pertinent to that organ. The icterus and biliruria (dark urine) which appear so regularly in this disease are unequivocally linked to the damage which the liver has sustained; anorexia, nausea, pain in the upper abdomen and vomiting point also to liver involvement; nor can such findings as abdominal tenderness, clay colored stools, pruritus, pyrosis, eructations, postprandial distress and flatus appearing in the course of this illness be considered in any other light. Conversely, it is well known that during the illness, especially at the onset there occurs fever, headache, chills, generalized aches and pains, coryza, sore throat, cough, chest pain, etc. It has been assumed heretofore that at least some of these symptoms—fever, chills, headache—are tied in somehow with the infection of the liver. Yet it is difficult to correlate this symptomatology with a syndrome specifically affecting the liver inasmuch as it is non-specific in character and appears to be no different from that common to various infectious diseases. Although the early symptoms, the fever, chills, etc., are relegated to the background by the more striking symptoms (jaundice et al) we feel that the relative importance of these

less specific manifestations should not be negated. To us the fever, chills, headache and upper respiratory findings (in this illness) appears to suggest the existence of a systemic disease such as influenza and related infections.

In support of the view that acute infectious hepatitis is a systemic process evidence of the occurrence in this illness of splenomegaly, lymphadenopathy and changes in the hematopoietic system will be presented.

THE SPLEEN

There is frequently mentioned in the literature splenic enlargement in acute infectious hepatitis. The large majority of these reports, however, point to a low incidence. We observed splenomegaly in 48 per cent of our patients by use of day to day percussion. The splenic and hepatic enlargement was usually present early in the course of the disease and the spleen decreased in size somewhat before the liver (as determined by percussion).

Our findings of a high incidence of splenomegaly in hepatitis are supported by the reports of Wayburn who found an enlargement in 11 of 20 cases of acute hepatitis and of observers in Palestine who found an enlargement in by far the majority of their patients.^{3,4} It is interesting that about three-fourths of the terminal cases of acute infectious hepatitis examined by Lucke⁵ presented an enlarged spleen at autopsy. He describes in the early stages of the disease a prominence of the lymphoid tissue which he ascribed to a cellular proliferation. In Lucke's opinion the same agent which damages the liver excites a similar reactive process in the spleen. An analogous simultaneous enlargement of the spleen and liver is observed in infectious mononucleosis (Landolt⁶).

The difficulty in perceiving moderate degrees of splenic enlargement by palpation is common to all clinicians. However, it is interesting that those authors who employed supplementary measures such as the roentgenogram (Finks and Blumberg¹⁰) or percussion (this author) in order to ferret out enlargement of this organ obtained significantly higher percentages of splenomegaly than they were able to attain by palpation. It is evident that the occurrence of splenomegaly in

acute infectious hepatitis is not a chance finding but rather an inherent part of the syndrome.

LYMPH NODES

Although our examinations during the icteric stage of the illness did not reveal lymphadenopathy the reports of other observers indicate its occurrence as a rule during the preicteric stage. Lymphadenopathy in the course of acute infectious hepatitis (according to Barker¹¹) is striking and frequent (81 per cent). Even in recurrent hepatitis the same author mentions the presence of low right-sided, deep cervical adenopathy. A clue to the pathologic nature of the lymphadenopathy can be gleaned from a statement of Fox¹² that the lymph nodes at times showed some reticuloendothelial hyperplasia at post mortem.

BONE MARROW

Alterations of the hematopoietic system in hepatitis has been recognized by many authors. There is no more complete description than that contained in the very excellent treatise of Jones and Minot (1923)¹³. They consistently noted in the peripheral blood a reduction in the number of red blood cells and of the hemoglobin which is most marked shortly after the height of the jaundice. There is usually an increase in the blood platelet count at this time. In our series of patients the average red blood cell count dropped to 3.5 to 4 million cells per cubic millimeter and the hemoglobin to 12-13 grams.

The total white count may be found increased slightly early in the disease but this is followed by a fall in the number of white cells. In our series the white count varied from 2450 to 9900 cells per cubic millimeter. As with the total white count the differential count is normal in the initial stage of the disease although a polymorphonuclear leucocytosis may occur. As the white count decreases there is an absolute rise in the number of lymphocytes and large mononuclears becoming most pronounced at the height of the jaundice or shortly thereafter when the lymphocytes amount to as much as 50 per cent and the mononuclears may reach 12 per cent of the total count.

The most characteristic feature of the white cell count is the occurrence of immature and abnormal lymphocytes and large mononuclears. Vacuolization of these white cells is commonly observed and with the associated lymphadenopathy and splenomegaly suggests a relationship to infectious mononucleosis, particularly since the latter condition is often associated with hepatic swelling and the presence of urobilin and urobilinogen in the urine (Landolt⁹). In our cases the Paul-Bunnell test was found invariably to be negative.

DISCUSSION

It is evident from this data that acute infectious hepatitis is characterized not only by pathologic involvement of the liver but also by concomitant changes in the spleen, the lymph nodes and the bone marrow. As mentioned previously this tends to substantiate the systemic nature of the symptomatology which ushers in the disease. Thus during the preicteric stage of

hepatitis there is often seen a sudden onset with frank chill or chilliness, fever reaching a daily peak of 102° F., sometimes 103-104° F., for a period as long as 4 to 5 days accompanied by headache, weakness, malaise and generalized aches and pains. At this time one finds the respiratory system affected frequently by rhinitis; sore throat, cough, chest pains and occasionally rales are present in the lungs. It is understandable that the diagnoses which are made on these patients at that time are not acute infectious hepatitis but influenza, upper respiratory infection, nasopharyngitis, tracheobronchitis and acute bronchitis.

It seems to us that the predominantly systemic symptomatology occurring with regularity at the onset of this illness is in conformity with the criteria of a virus infection. For example, it is well known that the non-specific symptoms, i. e., the chills, fever, myalgia, etc., herald the appearance of many, if not all, virus infections. Certainly the common occurrence in hepatitis of bradycardia, a relatively slow respiratory rate and leucopenia lend strong support to this assumption. Furthermore, the objective findings observed in the upper respiratory tract in our cases seem to differ little in character from those of influenza and other virus infections. Finally in harmony with our assumption on clinical grounds of a "virus type" of infection a preponderance of experimental and epidemiologic evidence points to a virus as the causative agent of acute infectious hepatitis.

It seems logical to attempt to correlate this data of the etiology, symptomatology and pathology in acute infectious hepatitis. The evidence of involvement of the spleen, lymph nodes, bone marrow and liver, shown above, seems to be quite conclusive. These organs constitute the principal components of the reticuloendothelial system. Inasmuch as a virus etiology can hardly be denied how does this agent fit into the pathologic picture? In addition to providing a basis to explain the non-specific, generalized symptomatology in hepatitis, viruses are known to exert a profound effect upon the reticuloendothelial system. Therefore, it follows that acute infectious hepatitis may be visualized as a disease of virus etiology with pathologic alterations in the component parts of the reticuloendothelial system.

If one accepts such a concept of acute infectious hepatitis as a disease of the reticuloendothelial system there remains to be explained the position of dominance which the liver assumes in the whole picture.

We believe that the liver of soldiers who develop hepatitis becomes markedly depleted of its protein and glycogen stores in the wake of the rigors of warfare. In at least 20 of our 53 patients there was obtained a history of having been in continuous combat for periods ranging from one month to as long as 10 months preceding the attack of hepatitis. These soldiers were obliged to subsist mainly on field rations during these combat periods. Over and above the fact that troops tend to lose their appetites in the heat of action they did not relish the field rations at any time and consumed only a fraction of it. To illustrate, some soldiers preferred the dinner ration and omitted

breakfast and supper; others selected cheese and crackers or a bar of chocolate, discarding the remainder. In other instances only spam and/or corned beef were available, and these soon became monotonous and were shunned entirely. The opportunity to partake of hot, palatable meals presents itself only rarely to combat troops. One patient was admitted to our hospital from a German prisoner of war camp where he had been confined for over three months and was forced to subsist on a diet composed of soup (made up of flour and water) and one slice of a poor-grade bread (yielding an estimated 423 calories). The weight on admission was 37 pounds below his normal. Many soldiers lost up to 25 pounds in a period immediately preceding the onset of the illness and some of them noted subjectively an increasing sense of fatigue.

From the above evidence it is apparent that the nutritional state of many soldiers in our series had already deteriorated at the time of their infection. The fact that there has been recorded an increased incidence of jaundice among soldiers in almost every war tends to confirm our observations of a close association between an inadequate physiologic state of the liver and the occurrence of liver damage. In World War II Cameron⁶ noted that there was a heavy incidence of the disease particularly following periods of active service in the field. Epidemics in our armies in the South Pacific and in the Mediterranean zones have been designated appropriately "campaign jaundice"¹⁴. In the South Pacific theatre many of the cases came from Guadalcanal during a period when combat fatigue and exhaustion were more pronounced than at any other time during hostilities¹⁵. Large numbers of cases were observed during the Napoleonic wars and this disease was also described during the American Civil War, the Franco-Prussian War, the Boer War and the First World War. The French have termed this disease "jaunisse de camps." (Dietrich¹⁶).

The direct effect of subminimal diets on the functional state of the liver is brought out strikingly in a recent work¹⁷. These authors noted an incidence of 67.7 per cent icterus in a group of Negro adults suffering from lobar pneumonia. They discerned the importance of malnutrition brought on by a diet of "fat side meat, corn meal, overcooked turnip greens, and sorghum" obviously deficient in protein and the vitamin B complex. These investigators simulated this diet in animals and proved that the complication of jaundice during the course of pneumococcus pneumonia appeared only in those animals in which a nutritional deficiency had been induced. In a series of hepatitis cases Fox¹² pointed out that the monotonous diets common to Espirito Santo make plausible the possibility in that region of a dietary deficiency as a predisposing factor.

The experimental production of liver changes by the employment of diets deficient in certain elements of the vitamin B complex supports a possible predisposition of the liver to damage by hepatotoxic agents^{18, 21}. Starvation for a period as brief as 24 hours has a profound effect in depleting the hepatic glycogen in a rat and also intensifies to a great degree the susceptibility

of the hepatic cells to injury by chloroform²². Moreover, it has been shown recently in animals that, in the course of protein depletion the liver loses protein²³, decreases in size and becomes soft and fatty. Addis, Poo and Lew²⁴ found that the loss of protein from the liver during a fast is much greater than the loss of protein of various organs and tissues of the body. In the presence of hypoproteinemia biliary obstruction, chloroform anesthesia and arsphenamine treatments cause much more injury to the liver cells than they do in the well-nourished patients or well-nourished animals. It would seem that the most probable deficiency responsible for the increased susceptibility to injury in the unfed animal or human, is its stores of protein which have been shown to be diminished in the body tissues and especially in the liver²⁴. "It is not just a flight of fancy to consider that the delayed liver injury as displayed by some human beings may be related to their dietary regime"²⁵. There can be little doubt that the liver of many soldiers, as those described here is so depleted of protein and glycogen that the immunologic response to infection is greatly impaired. It seems reasonable to assume that such a liver would be especially vulnerable to damage to its own structure.

The frequent occurrence of acute infectious hepatitis in patients convalescing from wounds, appendicitis and in the course of some other illness as malaria, diphtheria or scarlet fever, is well recognized⁶. Snell, Wood and Meienberg¹⁴ recognized that the disease was more severe and prolonged when it developed in soldiers under combat conditions in whom there was a background of malaria, dysentery or malnutrition. The onset of hepatitis in 11 of our patients in the course of their treatment for wounds and injuries is significant. At first one is apt to conclude prematurely that we were dealing solely with so-called "homologous serum jaundice," i. e., that the icterogenic agent had been introduced into the blood stream via the administration of blood or plasma. It is necessary to point out that these injured soldiers manifested over and above this several pertinent features bearing upon the ability of the body to withstand such an infection. Ever present in these convalescing soldiers was a history of combat and its attendant components insufficient food intake and fatigue (see above), loss of blood, the stresses of anesthesia and operations, and the administration of drugs, especially chemotherapeutic drugs. It is not too far-reaching to visualize that the exhausting effect of these factors on the protein, glycogen and vitamin content of the liver of a wounded man, should, at least theoretically, make him susceptible to any type of hepatotoxic agent.

In our series the incidence of other factors known to produce hepatic damage was quite low. Two of the patients gave a history of hepatitis prior to the present attack and three of the soldiers were undoubtedly alcoholics. Neither of these elements seem to be statistically significant in the pathogenesis of hepatitis.

One is able to reconstruct from this data what we visualize as the course of events in acute infectious hepatitis. First, the high incidence of this disease in armies, especially in combat troops with the accom-

panying inadequate intake of food, suggests the existence of malnutrition on a grand scale. Second, the result of under-nutrition is very likely a depletion of the normal content of protein and glycogen of the liver to the extent that the normal physiologic, which includes the detoxifying and immunologic, function is impeded. In other words, the liver would be susceptible to damage by toxins, sulfonamides, etc. A further drain on liver function may be imposed by the existence of draining wounds, fever and anemia. Third, infections are of course highly transmissible in large groups. The symptoms at the onset of this illness are generalized and nonspecific much as in any other virus infection and there is usually no clue that the liver is involved. Fourth, the reticulo-endothelial system, namely, the liver, spleen, lymph nodes and bone marrow appears to be the seat of the fundamental

pathologic changes in this disease. Finally, after the signs of infection, fever, upper respiratory signs, etc., have disappeared, there supervenes the stage of the disease in which the typical manifestations of liver damage predominate (icterus, biluria, etc.). In effect this hepatic stage heretofore has been considered as representative actually of the disease itself.

CONCLUSION

To conclude, acute infectious hepatitis may be viewed as a generalized infection of virus nature which attacks the reticulo-endothelial system — spleen, lymph nodes, bone marrow and liver. In cases such as in undernourished soldiers in whom the liver has been depleted of its protein and glycogen stores, there results the characteristic pathologic changes in the liver and associated symptomatology of this disease.

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Review of Disturbances of Fat Absorption and Fat Digestion

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ONE OF the most important functions of body fat is that of a concentrated reserve fuel which may be formed from any of the organic foodstuffs. Other functions of this depot fat are: protection from mechanical injury, prevention of rapid heat loss when exposed to cold, and its use as packing and support to visceral organs. Fats are readily stored, forming one of the main sources of energy, contain fat-soluble vitamins, and, by slowing the peristalsis of the stomach, produce a desirable sense of comfort and satiation.

Certain unsaturated fatty acids, linoleic, linolenic or arachidonic acid, have been found to be nutritionally essential, just as we consider certain of the amino acids essential, i.e., they cannot be synthesized at all or not in sufficient amounts by the organism. These fatty acids must therefore be supplied to the body by foods. Of interest are the observations of Burr that normal growth and health of rats requires the presence of certain unsaturated fatty acids in the diet of these animals. Evidence is accumulating that in human beings the addition to the diet of one of the above mentioned unsaturated fatty acids may have a beneficial and curative effect on eczematous children. The recent suggestion that the administration of unsaturated fatty acids improves resistance against the common cold, requires confirmation. Evans and Lepkovsky have shown the sparing action of fats on vitamin B in the rat.

Phospholipids and sterols are both essential to the normal structure of each cell as well as to functions of the body. Cell membranes are composed of protein and lipids, varying in kind and proportion, and apparently determining permeability, secretion, absorption, etc. Also, cell protoplasm is regarded as consisting primarily of proteins and lipids. Sterols and lipids compose the larger part of the entire nervous system. The bile acids and a number of hormones are sterols.

This paper will be limited to a discussion of the fats, their importance in nutrition, their digestion and absorption in the gastro-intestinal tract, and to the disturbances of these processes and their sequelae.

Fats are substances widely distributed in the animal and plant world. Having a content of carbon and hydrogen of 100%, they are the richest source of energy, liberating 9 calories per gram. Most of the fats used in human diets are of low melting point and therefore, are easily digested. The value of 9 calories per gram of fat represents the physiological fuel value

of fat, known as the Atwater and Bryant factor. In the calorimeter, when undergoing oxidation, fats yield 9.45 calories per gram, while the above physiological value allows for that part of fat lost in the processes of digestion and absorption. The often quoted value of Rubner, 9.3 calories per gram, was derived from experiments with dogs, and does not represent the loss in digestion as occurs in man on an ordinary mixed diet. This factor is of great practical importance in nutrition, for the fat in an average meal can supply about 20% of the necessary calories, thus diminishing the bulk of ingested food. This is of primary importance in instances of high energy requirements, such as hard work or in cold climates (Sherman, 1937).

Until recently it was believed that man, under normal circumstances and without hard work, could get along quite well on a very low fat diet, and experiments are reported in which subjects maintained themselves for six months on a diet containing only two grams of fat per day without any harm. Contrary to these experiments, experiences in Central Europe during the first world war conclusively showed that, when fat consumption is greatly restricted, premature hunger and reduced ability for hard work became apparent. The attempt to supply the needed calories by large amounts of carbohydrate produced discomfort and disability which was attributed to increased fermentation in the gastro-intestinal tract.

Fats may have harmful effects on the human body. There is no question that overfeeding of fat easily produces obesity in most human beings, a condition which may favor the development of metabolic disorders. Obesity and diabetes are frequently seen together, and from clinical experience it is a known fact that in patients with a mild diabetes weight reduction may bring about a clinical cure of the diabetes. The frequent occurrence of gout and obesity in the same patient is an old clinical observation. The concept of hypercholesterolemia as one of the causative agents in the development of arteriosclerosis is generally accepted today, although not proven conclusively. The results of older experiments, in which arteriosclerosis was produced in rabbits by a high cholesterol content in the diet, cannot be applied to man. Another factor against the latter concept is that, while prior to the advent of insulin the high blood cholesterol content was blamed for the high incidence of arteriosclerosis in diabetics, we can now prevent the hypercholesterolemia by proper management and yet, the incidence of arteriosclerosis in the diabetic has not decreased. Another group of metabolic disturbances in which restriction of fats is supposed to have curative effect, are certain xantho-

matoses, diseases in which due to unknown metabolic factors, there is an abnormal accumulation of cholesterol in the skin, tendon sheaths, muscles, and many other organs.

Fats and oils are neutral esters of a trihydric alcohol, glycerol, and consist of three fatty acid radicals and one molecule of glycerol. The prominent fatty acids of the human organism are palmitic, stearic, and oleic acid. Phospholipids are "substituted fats" containing nitrogen bodies and phosphorus; sterols, including cholesterol (the most important member), are unsaponifiable substances, have some of the physical properties of fats, but have no chemical relationship to them. The phospholipids are usually subdivided into lecithins, cephalins, and sphingomyelins. A sub-group may be included, called the glycolipids (cerebrosides, galactolipins).

During digestion and absorption of fats, a complicated mechanism is set into action involving nervous reflexes, humoral mechanisms (enterogastrone), secretion of bile, of pancreatic and of intestinal lipase, and a process of phosphorylation and resynthesis in the epithelial cells of the intestinal mucosa. In order to comprehend deficiencies of this mechanism, it is necessary to review briefly the fate of fat passing through the gastro-intestinal tract.

The first fat splitting enzyme encountered is the lipase of the stomach, which is present only in traces in the adult and probably plays no part in normal fat digestion. In infants, gastric lipase is supposed to play a larger part in fat digestion than in the adult. The most powerful fat splitting enzyme is secreted by the pancreas and, under normal conditions, supplies the larger amount of the enzyme. The secretion of this enzyme begins with the intake of food, increases when the ingesta enter the duodenum, and lasts for two or three hours. This secretion is partly controlled by a series of reflexes through the vagi (psychic reflexes), by chemical substances, and last but not least, by secretin and pancreozymin which are liberated from the mucosa of the upper part of the small intestinal tract. Secretin and pancreozymin, are carried from the small intestine by the blood stream to the pancreas and act by direct stimulation of the pancreatic cells. Mellanby's theory, still quoted in recent textbooks, that bile is essential in the absorption of secretin from the intestinal mucosa and thereby in the stimulation of pancreatic secretion, was disproved by Lueth and Ivy and by Thomas and Crider.

The pancreatic lipase is powerful enough to digest fat by means of splitting the largest part into glycerol and fatty acids; nevertheless, digestion and absorption of fat is normal only in the presence of bile. Bile enhances the action of lipase, increasing its splitting effect on fats; bile plus fatty acids emulsify the fat globules, reducing their size and lowering their surface tension; bile, by its hydrotropic property renders the fatty acids more soluble and better diffusible. During the interdigestive periods, bile is stored and concentrated in the gallbladder. The gallbladder bile is readily available for fat digestion and is discharged soon after the first chyme passes the pylorus (Pavlov's igniting

bile). The flow of bile is a continuous one. During digestion an increased volume of bile is delivered into the duodenum. This is due to two mechanisms. The first mechanism is due to the cholagogue effect of cholecystokinin, a substance present in the upper small intestine which is liberated by gastric chyme and which acts by stimulating the gallbladder to empty.

The second mechanism is largely due to the choleretic effect of gastric chyme and of bile salts. The greater part of the bile salts, after being secreted are reabsorbed, reach the liver via the portal circulation (enterohepatic bile salt circulation), and stimulate further secretion of bile.

The intestinal mucosa produces less lipase than the pancreas, but the intestinal lipase is important; thus in the absence of the pancreas, or ligation of its ducts, relatively large amounts of fat may be digested (Best and Taylor, 1945).

The process of fat absorption begins in the duodenum, and is practically completed in the lower jejunum. About 60% of the ingested fat can be recovered in the thoracic duct and the remainder in the portal circulation. The important work of Frazer has shown that so far as long chain triglycerides are concerned, as much as 60% of the absorbed fat may pass through the intestinal cell membrane as finely dispersed particles of unhydrolysed fat.

During the process of absorption fatty acids are resynthesised to neutral fats, but changed in character to more closely resemble the body fats. This resynthesis is preceded by the formation of phospholipids in the intestinal epithelium (a process called phosphorylation) and seems to be an active, vital property of the intestinal mucosa. Verzar's statement that the adrenal cortex controls this mechanism has been contradicted. Recent experiments have proven that defective fat absorption in adrenalectomized animals, or the steatorrhea found in Addison's disease, can be controlled by restoring the normal sodium and potassium balance by the administration of large amounts of sodium chloride, as well as by adrenal cortical extract (Pedvis, 1943).

Parts of the absorbed fats are used as a source of energy, while parts are carried to the fat depots of the body where they are stored and called upon in times of need. Smaller amounts become desaturated in the liver and are used for metabolic purposes of the body.

According to Schmidt and other authors, about 94% of the ingested fats are absorbed and only 6% lost in the feces, where they can be recovered as neutral fats, fatty acids, and soaps (see Anderson, 1945). These fractions occur in the feces in relatively constant proportions and, although there is a great range of variation, certain values have been accepted as standards. Schmidt, Fowweather, and Sperry, having done extensive research in this field, state that the average amount of total fat is about 18% of the dry matter of the fresh stool (dry matter being 21% of the fresh stool); cases with more than 25% have to be considered as pathological and indicate either deficient digestion or deficient absorption. Neutral fat constitutes 7% of the dry matter of the stool (42% of the total fat). Amounts larger than 11% (or more than

50% of total fat) lead us to suspect disturbances of fat digestion due to some pancreatic pathology. Fatty acids and soaps (together about 10% of the dry matter) should not exceed 15% of the dry matter or 75% of the total fat, higher figures being indicative of deficiencies in absorption. However, it should be borne in mind that, in order to conclusively prove abnormal amounts of fat in stools (steatorrhea) repeated examinations on a standard diet, like that of Schmidt, containing 120 grams of protein, 111 grams of fat, and 190 grams of carbohydrate, are absolutely necessary. Such standard diets are important because it has been shown of late that the normal gastro-intestinal mucosa is able to excrete fat itself even on a completely fat-free diet and during starvation (endogenous fat).

In cases of total obstruction of the pancreatic duct, and in severe deficiencies of absorption, fat can be seen microscopically, the stools having a characteristic greasy appearance. However, if the fat content of the feces does not exceed 30%-35% of the dry matter (20% is pathological), it may remain occult and it may have to be detected microscopically or chemically. For practical purposes stool smears are stained with Sudan III. Fatty acids show up as light orange tinted flakes, or as needle-like crystals which do not stain; soaps are seen as yellowish amorphous flakes, or as coarse crystals which do not stain; and neutral fats present themselves as deeply orange stained large and small droplets. With some experience it is possible to obtain with this method a clinically useful estimation of the relative amounts of the different fat fractions; however, in borderline cases, chemical procedures must be used.

According to the causative factors the disorders accompanied by abnormal fat excretion are classified into three main groups: Defects in the process of fat digestion, disturbances in fat absorption and one miscellaneous group. We propose the following clinical classification:

- I. Excess fat excretion due to defects in the process of fat digestion.
 - A. Steatorrheas associated with interference with bile secretion.
 1. Obstructive jaundice
 2. Disorders of the biliary system
 3. Biliary fistula
 - B. Steatorrheas due to pancreatic disorders.
- II. Excess fat excretion due to defects in the process of fat absorption.
 - A. Celiac disease
 - B. Non-tropical sprue
 - C. Tropical sprue
 - D. Chronic morphine poisoning or phlorhizin
 - E. Addison's disease
- III. Excess fat excretion associated with miscellaneous disorders.
 - A. Rapid passage of material in the gastro-intestinal tract (e.g. diarrhea, gastrectomy).
 - B. Blockage of lacteals

1. Tuberculous enteritis
2. Mesenteric lymphadenitis
3. Tumors involving the mesentery

C. Diminished absorptive surface of the small intestine (e.g. malrotation with short small intestine; generalized polyposis, etc.)

Ad. 1-A. The complete or partial lack of bile in steatorrheas due to defective bile secretion makes adequate absorption impossible in spite of the presence and activity of the lipolytic enzymes. Large quantities of neutral fat, fatty acids, and soaps in relatively normal proportions appear in the stools, giving them a characteristic greasy appearance. The absence or the presence of bile pigments and their derivatives in the stool and in the duodenal content are important differential diagnostic features in these conditions.

Ad. 1-B. Pancreatogenous steatorrheas with deficient secretion of lipase may be due to pancreatic cystic fibrosis, to pancreatic duct stones, to compression of the pancreatic ducts, to sequelae of acute inflammations of the gland, or it may accompany (more often than commonly believed) chronic inflammation of the biliary system extending to the pancreas. The loss of fat in these conditions may be severe. When stools are allowed to stand, neutral fats, the largest part of the total fat in these cases, separate out as a yellowish oil. In mild cases, steatorrhea may be occult and must be detected by laboratory examination.

The work of Farber on pancreatic steatorrhea has furthered our knowledge on this subject. From children showing obstructive pancreatic lesions at autopsy, Farber separated three clinical groups:

Group 1. Infants who died in the first week or first few weeks of life from meconium ileus. The ileus is attributed to a lack of pancreatic enzymes in intrauterine life, lack of liquefaction of the meconium by the enzymes and subsequent inspissation of the meconium. The intestine is unable to propel the thick meconium through its lumen, with resulting intestinal obstruction.

Group 2. Infants who died, usually in the first year of life, with a clinical history of nutritional disturbance often obscured by respiratory disease, usually called chronic pneumonia, bronchitis, or bronchiectasis. Three explanations for the pulmonary lesions have been offered. First, decreased resistance in a patient chronically ill and with nutritional failure. Second, vitamin A deficiency with metaplasia of bronchial epithelium and secondary infection. It seems that this mechanism plays a role only in cases with a marked degree of vitamin A deficiency. Third, a generalized deficiency and abnormality of mucus production involving all mucus secreting glands, especially in the bronchial tree and in the pancreas, where inspissated mucus produces pancreatic obstruction and subsequent cystic degeneration of the pancreas, formation of bronchiectases and infection in the bronchial tree.

Group 3. Cases of pancreatic deficiency with indefinite symptoms wrongly diagnosed during life as preceliac or celiac disease. The patients die of respiratory disease and autopsy reveals obstructive pancreatic le-

sions. The age ranged from six months to fifteen years. The terminal respiratory disease may be incidental or may be due to the factors mentioned under group 2.

In the three groups of Farber discussed above, besides the pancreatogenous steatorrhea, there is another important diagnostic feature, namely, the presence in the stools of large numbers of undigested muscle fiber (creatorrhea), and the increase in fecal nitrogen beyond 8-9% (azotorrhea). Creatorrhea and azotorrhea are due to deficient secretion of trypsin by the pancreas. In cases of chronic pancreatitis, in which lipase deficiency may be difficult to detect, the presence of creatorrhea or azotorrhea is pathognomonic. Additional diagnostic aids are duodenal aspiration with assay for pancreatic enzymes and the newly developed secretin blood enzyme test.

In steatorrheas of long standing, regardless of their etiology, important systemic findings occur. They are emaciation, anemia, hypocalcemia, tetany, osteoporosis, liver damage, and bleeding tendency. These changes, being characteristic of all steatorrheas, will be discussed later.

Ad. II. In the second group of steatorrheas pancreatic function is normal, but the intestinal absorption of fat is disturbed. In spite of the presence of bile and pancreatic lipase in the small intestine and in spite of their normal or nearly normal digestive action, the absorption of fats is so severely interfered with by factors not yet well understood, that large quantities of neutral fat, fatty acids and soaps are excreted in the stools. Bile and its derivatives are always present in the stool in these conditions. Three diseases, formerly thought to be separate entities, belong to this group: celiac disease, nontropical sprue, and tropical sprue.

Samuel Gee, of London, was the first to describe, in 1888, a condition in children called celiac disease. Gee's description of the disease, in which he also mentions that it may occur in adults, was forgotten until Herter in New York and Lehndorff in Vienna simultaneously reported and gave an excellent description of this syndrome in children.

A disease with similar symptomatology in adults has been called non-tropical sprue because of its similarity with tropical sprue. The existence of non-tropical sprue was very long disputed and only in recent years, thanks to the excellent work of Thaysen in Copenhagen, the existence of a non-pancreatic steatorrhea in non-tropical countries was accepted. Thaysen advocated the idea that celiac disease, non-tropical and tropical sprue are different forms of one and the same entity, and proposed calling them, until their etiology and pathology became better understood, idiopathic steatorrheas.

Today, following the suggestion of Moore, celiac disease in children is called Gee-Herter's disease, the idiopathic steatorrhea in non-tropical countries is called Gee-Thaysen's disease, and the name sprue is retained for the disease occurring in the tropics.

It is believed that, although these three diseases seem to be the same clinical entity, the etiologic factors may

not be quite similar in all; or it may be that the symptoms vary in degree, due to different responses of the child's or of the adult's body to the same factors, but under different conditions and in different environments.

The primary fault in this group of diseases is an imperfect intestinal absorption of fats, due to disturbed functions of the absorbing intestinal epithelium, possibly deficient phosphorylation. The underlying cause is not definitely known, and no concept exists today clarifying the involved etiological and pathological factors, although some nutritional or vitamin deficiencies seem to be involved. The belief that monilia psilosis is the infective agent in tropical sprue has been disproved.

The prominent symptoms common to all three diseases are metabolic disorders. The latter are characterized firstly by abnormally large quantities of fat excreted in the stools, secondly by normal or slightly increased nitrogen excretion, thirdly by a flat oral blood sugar curve, and fourthly by an elevated basal metabolism; the latter seems strange in conditions where the opposite is to be expected. Steatorrhea which is constantly observed in the acute stages of the disease, may be less in amount or occult in early or latent stages.

The normal, or only slightly raised nitrogen excretion differentiates these steatorrheas sharply from those produced by diseases of the pancreas, in which the excretion of nitrogen in the feces may reach 20 grams against a normal of 1 gram per day.

A flat blood sugar curve following the oral or i.v. glucose tolerance test is a nearly constant symptom in Gee-Herter's disease and is also frequent in Gee-Thaysen's disease and in tropical sprue. This flat curve usually disappears in latent stages, but it may persist. Thaysen thinks that it is due to some disturbance in the regulatory mechanism of the blood sugar. The assumption that in these patients a defective absorption of carbohydrates might parallel defective fat absorption is disproved by the finding of a respiratory quotient increased to one or nearly one after the intake of carbohydrates.

The elevated basal metabolism is not so constant as the other symptoms, but occurs in more than 50% of the cases and is probably caused by some disturbance of endocrine glands. Only in advanced cases with severe emaciation is the rate low.

The above mentioned metabolic disorders can hardly be found simultaneously in any other disease, and are therefore very characteristic.

An additional finding is a disorder of the calcium-phosphorus metabolism with consequent clinical symptoms. It must be remembered, however, that these symptoms are not only characteristic of steatorrheas with defective absorption, but are also found though to a much lesser degree, in steatorrheas of pancreatic or biliary origin. The calcium-phosphorus disarrangement is partly due to the loss of calcium which combines in the intestines with fatty acids to form insoluble calcium soaps, and partly to an avitaminosis D, resulting from defective absorption of fats carrying this vitamin. The resulting clinical symptoms of these

disturbances may be skeletal changes such as dwarfism, bone decalcification, spontaneous fractures, osteomalacia, tetany, cataract, and pain and tenderness of the bones. These are most commonly observed in Gee-Herter's disease in children because of the sensitivity of this age to disorders in calcium metabolism (Snell and Camp, 1934).

In adults with non-tropical sprue severe sequelae of calcium-phosphorus imbalance are relatively rare because of the large store of calcium and phosphorus in the adult bone system; they are not found in tropical sprue, due possibly to the beneficial effect of strong sunlight.

Blood pictures are rarely normal; tropical sprue shows a macrocytic hyperchromic anemia which may be so severe as to be mistaken for pernicious anemia. In Gee-Herter's and Gee-Thayssen's disease a microcytic hypochromic anemia is the rule.

Avitaminosis B, deficient absorption of the anti-anemic principle and of iron, are the causative factors of these anemias. Symmetrically arranged pigmentation of the skin is probably due to deficiency of vitamin B. Increased prothrombin time with a tendency to bleeding has been reported lately and is the result of a defective absorption of the fat soluble vitamin K.

Gastro-intestinal symptoms include a glossitis in cases with hyperchromic anemias, very often an absence of hydrochloric acid in the fasting stomach, but a positive response to histamine, and intermittently occurring diarrhea with voluminous watery, greasy, foamy, malodorous stools.

An interesting finding is a dilatation of the colon, accompanied by a pronounced sacculatation of the entire large intestine, most likely due to atony. Dilatation

The authors are indebted to Dr. H. Necheles for advice and help.

of the small intestine with a peculiar segmentation of barium contents observed by Kantor seems to be due to the accompanying vitamin B deficiency.

Steatorrheas produced by phlorhizin belong to the group with defective absorption and are probably due to a disturbed process of phosphorylation in the epithelial cells of the intestinal mucosa. Steatorrhea in Addison's disease and in chronic morphine poisoning are probably of the same origin.

Ad. III. In the third group are included steatorrheas following resection of the stomach and cases of enteritis, where impaired digestion and absorption results from increased motility of the upper intestinal tract. Forges has described a disease which he named ileitis without colitis, abnormal amounts of fecal fatty acids and soaps being the outstanding features. Blockage of lacteals by chronic inflammations, granulomas and infiltrating tumors, leads very often to steatorrhea. Cases of steatorrhea have been reported in which congenital short intestine or polyposis of the entire small intestine were considered to have altered the absorbing surface to such a degree that normal fat absorption was interfered with.

In conclusion, let us again emphasize that a thorough knowledge of the physiology of fat digestion and absorption is essential to an understanding of the previously mentioned disease process. With this knowledge, plus the diagnostic aids at hand, many previously mysterious steatorrheas may be recognized. And lastly, the recent important work separating pancreatic cystic fibrosis as a distinct entity from the group of celiac disease, tropical sprue, and non-tropical sprue has been a big factor in furthering our knowledge, diagnosis, and therapy of many cases of steatorrhea.

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Book Review

Differential Diagnosis of Jaundice. By Leon Schiff, Ph. D., M. D., pp. 313, The Year Book Publishers, Inc., Chicago, Ill., \$5.50.

To know the cause of jaundice in a given case is of primary importance and usually difficult. Once the cause is known the method of treatment naturally follows. The present useful and practical book confines

itself to the diagnostic problems involved and clarifies the confusion which exhaustive texts and the new knowledge have given to the subject. Schiff has been known for the fundamental value and the originality of his work in gastro-enterology for many years, and this book is comparatively brief, seasoned with the judgment of a teacher, and above all, timely. The sub-

ject of homologous serum hepatitis is adequately dealt with. A chapter on clinical and laboratory aids in diagnosis is particularly valuable. This book is needed by every internist.

Handbook of Diet Therapy. By Dorothea Turner (for the American Dietetic Association). Pp. 112 (\$2.00), The University Chicago Press, Chicago 37, Illinois, 1946.

The book is particularly valuable to the physician, the student and the dietitian, because it covers normal diet and those conditions of disease which may require therapeutic diets, and it gives the reader a new facility in figuring required diets. The reliability of the treatments offered, plus the simplification of the methods of diet calculation, render the volume of exceptional value. The glossary of dietetic terms, which was created after years of study, will minimize confusion by strict definitions.

Hygiene, 4th Edition. By Florence L. Meredith, Pp. 838 (\$4.00), The Blakiston Company, Philadelphia 5, Pa., 1946.

Anybody, including physicians, will profit by and be interested in reading this book. It should prove vastly interesting to a person of intellectual curiosity who, without special medical education, desires to have reliable information on an array of topics, all of which pertain to the individual, social and national health. Here may be found everything from intestinal peristalsis and sick headache, through phagocytosis and bacteriophage to parenthood and psychoneurosis. The

section on the Self Impulse was worth reading because, for the first time, the reviewer was able slightly to clarify his apprehensions with respect to the significance of the closely related terms, ego, superego and Id. The book has a definite savor of psychology and a pleasant aroma of philosophy bestowed by one who apparently knows the technical details of how life should be lived, the self (or Id) controlled, and happiness attained. We recommend it to those who crave a general medical orientation, particularly readers of medical columns because the book is reliable.

EARLY AMBULATION (and Related Procedures in Surgical Management). By Daniel J. Leithauser, M. D., F. A. C. S., Pp. 232 (\$4.50). Charles C. Thomas, Springfield, Illinois.

Among 2047 early ambulatory cases, 840 of the patients were out of bed in 3 to 4 hours after operation. By promoting dynamic physiological restitution through early ambulation, post-operative illness is minimized, complications reduced or avoided and rapid recovery promoted. Functional crippling of the gastro-intestinal tract, the respiratory and vasomotor systems seem thus to be prevented. Walking is the most valuable post-operative procedure. Defiance is shouted to the traditional cautions, and, judging from the author's careful observations, not without complete justification. The new conception fits in well with present crowded hospital conditions and the present impatient temper of modern man. Follow Leithauser and form your own opinions.

Abstracts of Current Literature

(Microfilm copies of papers may be obtained from the Medicoilm Service of the Army Medical Library at 25c per each complete article, not exceeding 25 pages in length—and 10c for each additional 10 pages or fraction thereof. Prepayment is not requested. Remittances may be made with subsequent orders and in such manner as found most convenient. Address—Medicoilm Service, Army Medical Library, Washington, D. C.)

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Progress in Gastrointestinal Physiology — Abstracts from the Federation Proceeding for 1944 and 1945

By

I. H. DOUGHERTY, B. S., and JOHN MOFFITT, M. D.

The following are abstracts of papers in experimental physiology of gastric secretion and gastrointestinal motor activities which appeared in volumes 4 and 5 of the Federation Proceedings. This is the publication of the Federation of American Societies for Experimental Biology. The numerals in brackets following the authors' names refer to the respective vol-

ume and page of the Proceedings.

GASTRIC SECRETION

The effect of electric current on gastric secretion and potential was investigated by Rehm (4:58). When current was sent from the serosa to the mucosa in the secreting stomach there was an increase in the rate

of secretion followed by a relatively rapid return to the original rate. When applied in the opposite direction there was a decrease in the secretion followed by a much slower return to the original rate. Following this latter procedure the potential differences across the stomach were depressed and there was a close parallelism between the recovery of the potential and the secretory rate. Application of current in either direction to the non-secreting stomach did not result in secretion of hydrochloric acid. Using anesthetized dogs, Rehm (5:85) also found that changes in the potential difference set up between the submucosal and mucosal electrodes closely paralleled that between the serosal and mucosal electrodes. Thus, the major portion of the gastric potential originates between the submucosa and mucosa.

The influence on gastric secretion of fluids introduced into the intestine was studied by Friedman, Pincus and Thomas (5:30). Instillation of a volume of liquid (water, physiological saline, or 0.1 N HCl) resulted in an increase in volume of gastric secretion only when the gastric glands were already excited by food, insulin, or histamine. They found that the extent of increase was related to the volume of fluid introduced and not to the degree of preceding inhibition. Ogden and Southard (5:77) studied the influence of wine on gastric acidity in eight normal male students. Results showed that wine increased both the free and total acidity, and the peaks were prolonged. Alcohol effects resembled the wine in intensity and peak but rose and fell more rapidly. Acid or dealcoholized wine gave little rise but this rise was sustained for a long time. This may account for the less violent but more sustained stimulation of gastric secretion which wine gave in contrast to alcohol.

Calcium in gastric mucus was studied by Hollander and Lauber (5:49), using emulsions of eugenol and mustard oil as contact stimulants to obtain mucus secretion from the Heidenhain pouches of dogs. The mean calcium content was 10.31 ± 0.10 mg. per 100 ml. Treatment with 0.1 N HCl in vitro removed all the calcium from the insoluble portion of the mucus.

In experiments with pentobarbital anesthetized dogs with whole stomach pouches, Kurtz and Clark (5:188) found that following perfusion of carbon dioxide-free air or nitrogen, the HCl secretion in response to histamine was in inverse proportion to the carbon dioxide diffused into the stomach lumen, and thus to the mean carbon dioxide tension of the gastric tissue and blood.

Using dogs which had either hypophysectomies or thyroidectomies plus oophorectomies, Kaulberz, Patterson, Sandweiss, and Saltzstein (5:54) studied the effect on gastric secretion of urine extracts obtained from dogs having various endocrine organs extirpated. Urogastrone from normal dogs inhibited gastric secretion less often than did that from operated animals having thyroidectomies plus oophorectomies. Inhibition of secretion was greatest in animals having thyroidectomies plus oophorectomies when treated with urine extracts from hypophysectomized dogs. Hypophysectomized dogs showed more gastric inhibition when given extracts from hypophysectomized dog's

urine than when given extracts from a normal dog's urine.

Clark, Adams, and Romano (4:114) studied the following antacids on gastric secretions: Sodium bicarbonate, aluminum hydroxide gel, calcium carbonate, and magnesium oxide. Sodium citrate was used in the control series. Sodium bicarbonate and calcium carbonate produced the greatest and most consistent increases in secretion. In general none of the antacids produced a significant decrease in secretion during the nine-hour period following the test meal. Krantz, Jr., Kibler, and Bell (4:125) prepared an aluminum dihydroxyaminoacetate which was found to have a prompt and prolonged buffering effect on acid and to be very useful in the treatment of hyperacidity and peptic ulcer. This compound was 42% more efficient in acid-consuming power than dried aluminum hydroxide gel.

Bucher (4:10) found pepsin in the urines of 25 normal young women. The pepsin concentration in any single sample correlated well with its specific gravity. Highest peptic potencies occurred in specimens with low pH (4.5 to 5.0). Studies by Milhorat (4:51) have shown that oral administration of tocopherol that previously had been incubated in the stomach of a normal man can reduce the creatinuria of patients with progressive muscular dystrophy, whereas the untreated vitamin was without effect. When the administration of an extract of hog stomach and duodenum was discontinued there resulted an immediate decrease in the output of creatine although the effect during the period of administration was not marked.

GASTRIC MOTOR ACTIVITIES

Sturgeon, Henschel and Keys (4:68) by using an oatmeal-barium test meal on normal men who were maintained on various diets could find no significant influence of the diet on either the rate of gastric emptying or the final emptying time. Northup and Van Liere (4:54) concluded that the delay in gastric emptying in normal men due to a glucose meal was in proportion to the concentration of glucose. Thus the average emptying time with the control meal was 2.23 hours, with 25 gms. of added glucose 2.76 hours, 50 gms. of added glucose 3.09 hours, and 75 gms. of added glucose 3.36 hours. By x-ray examination after a barium meal Hemingway (4:33) found there was both a loss in gastric tonus and a delay in gastric emptying as the result of experimentally induced motion sickness in normal young men. The effect of 6 months semistarvation on the gastric emptying time of human males was studied by Henschel and Sturgeon (5:45). They found, by means of fluoroscope and x-ray, that there was usually a longer emptying after starvation. Before starvation the emptying time was 175 ± 32 and after starvation it was 226 ± 70 minutes with a significant mean of 51 minutes. Of 18 subjects, 11 had an increased emptying time, 6 had no change, and 1 had a decreased emptying time. Gastric motility seemed depressed during emptying with the greatest depression occurring at 90 minutes.

The effect of chloral hydrate administered just prior

to ingestion of a test meal of barium sulphate was studied fluoroscopically by Northup and Van Liere (5:77). They found that 0.6 gm. chloral hydrate has a slight but definite effect in stimulating gastric emptying in 11 out of 12 cases, of which 3 had a statistically significant hastening of emptying. In a study on anesthetized dogs Stavrakys (4:67) found that intra-arterial administrations of acetylcholine often greatly increased the motility of the stomach. In several experiments an hour-glass contraction of the stomach developed, completely separating the pyloric region from the body of the stomach so that simultaneously, alkaline mucus was collected from the former and acid gastric juice from the latter.

In attempting to explain the diminished rate of fat absorption in rats subjected to an oxygen pressure of either 63 mm Hg or 53 mm Hg, MacLachlan (5:66) administered 1.385 gm. corn oil to previously fasted albino rats kept at 53 mm Hg oxygen pressure for 2, 3, or 4 hours. Significantly less fat was found present in their stomachs at the end of 2 and 3 hours than in controls kept at atmospheric pressure. Since no difference in fat content was found at 4 hours, it was concluded that there was an initial acceleration in the rate of stomach emptying in rats as a result of the reduced oxygen tension.

INTESTINAL MOTOR ACTIVITIES

McClendon (4:50) reported that sodium acetate stimulated both longitudinal and circular muscle activities of the isolated intestine of the rabbit and rat. The action was presumably on the serosal side of the muscle since everted muscle segments were not affected.

Stichney, Northup and Van Liere (4:68) studied the influence of blood sugar levels on the distance a marked meal traverses in the intestine of unanesthetized dogs. They found that hypoglycemia retarded the motility of the small intestine by about 23 per cent. The influence of certain antispasmodics on postprandial intestinal activity was investigated by Wakim (4:74). When given after a meal all of the antispasmodics studied, except papaverine, delayed intestinal activity as measured in intact intestinal loops of trained unanesthetized dogs. Included among the drugs were: amyl nitrite, aminophylline, octin hydrochloride, traserentine, and demerol, the latter being unusual in first causing increased activity with defecation, then a depressant action resulting in complete cessation of intestinal motility for a half hour.

The effectiveness of new antispasmodic esters against intestinal spasm induced by histamine was studied in guinea pig ileum in vitro by Treischer-Elam (4:138). Phenyl (Alpha)-thienyl-glycolate was found to be four to five times as effective as traserentine in relaxing histamine contraction; the phenyl (Alpha)-thienylacetate was equal to traserentine while pavatrine was 0.5 to 0.8 as active. On guinea pig ileum the hydrochloride of (Beta)-piperidinoethyl methyl-p-xenylacetate was half as active as traserentine against histamine-induced spasm, but caused greater amplitude of rhythmic contraction. Cantoni and Eastman (5:169) found that isolated strips

of guinea pig ileum suspended in Tyrode's solution showed a decreased ability to contract following maximal contraction due to large doses of acetylcholine, pilocarpine, or barium chloride. This refractory period lasted about 30 minutes. Following a maximal contraction caused by KC1 there was no refractory period following a previously effective dose of histamine or acetylcholine, but rather a period of heightened response to these and other agents. The antispasmodic effects of (Beta)-dimethylaminoethyl benzilate HCl were studied by Wakim, Powell, and Chen (5:210), who found that in trained dogs with a skin-covered intestinal loop (continuous with the gastrointestinal tract and with circulation and nerve supply intact) the drug abolished peristaltic and rhythmical segmentation movements for periods roughly corresponding to the amount of the drug used. This marked effect was manifested both following feeding and treatment with prostigmine, physostigmine, or pilocarpine. Yonkman, Hays, Cameron, Pellett, and Hansen (5:216) found that the ileum (Thiery-Villa loop) of dogs was markedly stimulated by 0.5-2.0 mg. of pascal administered intravenously. This ileal activity could be prevented or corrected by doses of atropine sulphate or traserentine by most routes of injection. Hazleton and Godfrey (4:124) report on a method for studying drug action on isolated segments of mouse intestine. The drugs are applied to either within the loop or else externally. Results analogous to oral or parenteral administration of the drugs to intact animals are said to be obtained.

Bozler (4:8) found that the action potentials of the stomach and intestine in most species have a long plateau. High concentrations of adrenalin stop the action potentials and motility but, with smaller amounts of the drug, rhythmic potentials may be present while contractions are not detectable visually. The action potential of intestinal mucosa and the simultaneous pressure changes within the lumen of Thiery jejunal fistulae in unanesthetized dogs were studied by Youmans and Foltz (5:116). By means of an oscilloscope the authors found a slow, smooth, potential change beginning at 0.8 sec., 0.4 sec. prior to the beginning pressure increase due to rhythmic contraction. During the pressure rise there were numerous medium-fast potentials. These potentials were accentuated by choline derivatives and physostigmine, and were eliminated by atropine and adrenalin. The medium-fast waves were interpreted as smooth muscle action potentials while the slow, smooth, potential changes were of unknown origin.

Friedman and Snape (5:30) recorded the color changes in the mucosa of the colon in children as affected by food and psychic stimuli. The children, ages 4, 9, and 10 years, had established colostomies and were in excellent health. The color changes of the mucosa were noted by direct inspection and by matching with color standards of a hemoglobin scale. Their observations were as follows: Mild, painful stimuli, verbal suggestion of pain, or discussion of unpleasant past experiences all gave rise to mucosal blanching. Sight or smell of appetizing food and the act of eating produced a marked reddening and engorgement

of the mucosa. Stool extrusion was followed by a marked engorgement although during the process the mucosa remained pale.

Necheles, Walker, and Olson (5:75) reported that colonic motility was usually increased following hemorrhage in unanesthetized dogs with chronic fistulas and in dogs anesthetized with pento-barbital sodium, morphine-barbiturate, or ether, regardless of the size of the hemorrhage. The upper gastrointestinal tract usually showed a slight decrease in motility while the ileum showed little or no change in motility. Colonic hypermotility was noted regardless of the nature of the anaesthetic used. These workers believe that colonic hypermotility following hemorrhage was not due to systemic blood pressure fall, but to local vasomotor constriction or to an increased number of parasympathetic impulses.

Hoekstra and Steggerda (5:48) reported that in dogs with permanent opacity of the colon (due to thorotrast) there was a proportionate increase in colonic activity, either in increased amplitude, increased frequency, or a combination of both following intracardial injection of 0.1 to 2.9 mg./kg. of pyribenzamine. Usually an increase in muscular tone was noted concomitant with the above. Steggerda, Richards, and Hoekstra (5:101) showed that there is a synergistic effect on postprandial colonic activity in normal human males following administration of antispasmodic compounds and nembutal. Manometric tracings of colonic pressure in an air-distended colon indicated that oral administration of 100 mg. of amethone (A. P. 43) inhibited activity after approximately 30 minutes and inhibition lasted about 40 minutes. Nembutal (25 mg.) increased the effective inhibition period by about 50%.

EXPERIMENTAL MEDICINE

SECRETION

SHAY, H., KOMAROV, S. A., SIPLET, II., AND FELS, S. S.: *A gastric mucigogue action of the alkyl sulfates.* (*Science*, v. 103, p. 50, 1946.)

Anesthetized dogs with gastric fistula and the pylorus ligated were used. Sodium lauryl sulfate and sodium dodecyl sulfate were introduced into the stomach. When the gastric contents were subsequently drained they were found to contain mucin and chlorides. Some evidence of resorption from the gastric lumen was obtained. The secretion of mucin persisted for several hours after withdrawal of the stimulating agent and was not abolished by atropine.

ABSORPTION

FRAZER, A. C.: *Effect of choline on the intestinal absorption of fat.* (*Nature*, v. 157, p. 414, 1946.)

Rats were fed by stomach tube 1 cc. of water and 1 cc. of olive oil. The cells of the intestinal epithelium became filled with large fat globules but little fat apparently passed into the villus or lymphatic lacteals.

After feeding 1 cc. of olive oil with 1 cc. of 0.5 percent choline, the fat appeared readily in the villus. The globules in the epithelial cells were also less gross.

PATHOLOGY

JACOBSON, W. AND WILLIAMS, S. M.: *Use of splenectomized rabbit for assay of liver extracts.* (*J. Path. Bacteriol.*, v. 57, p. 423, April, 1945.)

Various livers and digestive tract organs were assayed for reticulocyte response in splenectomized rabbits. Purified liver extracts gave responses indicative of their anti-pernicious anemia potency. Extracts of small intestine, particularly villi and crypts of Lieberkuhn, as well as of carcinoid argentaffine tumors of the mucosa, were active in inducing a reticulocyte response. It is concluded that the argentaffine cells are the source or storage cells of the anti-anemic principle in the mucous membrane.

BARONOFKY, I. D., AND WANGENSTEEN, O. H.: *Role of nitroglycerine in accelerating occurrence of histamin-provoked ulcer.* (*Proc. Soc. Exper. Biol. Med.*, v. 62, p. 127, June, 1946.)

Nine of twelve rabbits given both nitroglycerine and histamine from one to 26 days developed ulcer and/or erosions. No ulcers occurred in the control animals (3 receiving histamine and 3 receiving nitroglycerine). All of the four dogs receiving both histamine and nitroglycerine developed ulcers within three to seven days (time of sacrifice), but three dogs which received histamine alone had no ulcers. On dogs with either a Heidenhain or a Pavlov pouch, no stimulation of volume or of free HCl was observed as a result of aqueous nitroglycerine subcutaneously. It is believed that the effect of the nitroglycerine is due to its venous pooling property. This, coupled with normal arteriolar reflex contractile responses, results in areas of impaired circulation, which are then subjected to acid-peptic digestion.

NEAL, M. P.: *Fat Necrosis studies: The effect of feeding lipase-containing vegetable seed on the production of fat necrosis.* (*Arch. Pathol.*, v. 41, p. 37, 1946.)

Peanuts and soy beans are seeds containing high amounts of lipases. To test the hypothesis that lipase in the diet may be responsible for fat necrosis, these vegetable seeds were fed raw to rabbits, rats and pigs. The results were negative.

OPIT, E. T., AND LAVIN, G. I.: *Localization of ribonucleic acid in the cytoplasm of liver cells.* (*J. Exper. Med.*, v. 84, p. 107, July 1, 1946.)

The technique of ultraviolet microscopy described by Lavin was used because tissue components such as nucleic acid, nucleo-proteins, and proteins have absorp-

tion bands in the ultraviolet region of the spectrum. The microphotographs of unstained sections bear an astonishing resemblance to those of sections stained with nuclear dyes. In the cytoplasm of liver cells, a basophilic substance occurs in two forms which are described. This material accumulates beyond normal in association with hyperplasia of the liver cells and also of newly formed bile ducts in response to the administration of dimethylamino-benzene (butter yellow) to rats. The substance is thus found in hepatomas and cholangiomas produced by butter yellow. In both normal tissue and in these tumors, it has the characteristics of ribonucleic acid, and absorbs the ultraviolet radiation of wave length 2537 Å. It does not give the Feulgen reaction, and it is removed from the cytoplasm by ribonuclease, precipitation with lanthanum acetate protecting it against the enzyme.

METABOLISM AND NUTRITION

HEGSTED, D. M., TSONGAS, A., ABBOTT, D. B., AND STARE, F. J.: *Nitrogen balance and protein requirements of adults.* (*J. Lab. Clin. Med.*, v. 31, p. 261, March, 1946.)

The nitrogen requirements of 26 healthy adults were studied. When on low protein diets the requirements were related to the surface area of the patient rather than his body weight. To maintain nitrogen balance an intake of 2.9 grams nitrogen per square meter of surface is required. Proteins of low efficiency were adequate to meet nitrogen requirements only if given in large amount. A daily intake of 50 grams of protein should provide a sufficient excess above the minimal needs in persons in good health.

HAWINKO, L., AND SPRAGUE, P. H.: *Treatment of obesity by appetite-depressing drugs.* (*Canadian Med. Assoc. J.*, v. 54, p. 26, 1946.)

D-amphetamine was found an extremely useful depressant of appetite in patients who were treated for obesity by dietary restriction. A dose of 2.5 milligrams one hour before each meal was prescribed while the patient was on a diet of 1,100 calories. The drug reduced the irritability and mental depression which

patients on reducing diets frequently show. Vitamins and thyroid substance in patients with metabolic rates below 0, were also given. The amphetamine was increased as indicated to a maximum daily dosage of 15 milligrams.

Patients overweight by more than 100 pounds lost 7.6 pounds per month, patients overweight by less than 50 pounds lost 4.7 pounds per month. The monthly average loss in weight was 5.5 pounds in 72 patients.

SIEGAL, S.: *Benign paroxysmal peritonitis.* (*Ann. Intern. Med.*, v. 23, p. 1, 1945.)

Benign paroxysmal peritonitis is a clinical syndrome with the principal lesion involving a reversible vascular reaction mainly in the peritoneal subserosa. The clinical picture is distinctive; bouts of severe pain, fever, abdominal tenderness and sometimes abdominal wall spasm. Chest pain suggestive of irritation of the diaphragm or pleura may be present. The condition is generally misdiagnosed as an acute surgical lesion. The etiology and pathologic basis of the disease is unknown. Food allergy may be suspected but probably will be ruled out by further study.

MISCELLANEOUS

WATSON, C. J., AND HAWKINSON, VIOLET: *Semi-quantitative estimation of bilirubin in the urine by means of the barium-strip modification of Harrison's test.* (*J. Lab. Clin. Med.*, v. 31, p. 914, Aug., 1946.)

Sheets of thick retentive filter paper are immersed in a saturated aqueous solution of barium chloride, then after drying are cut into strips. A strip is inserted so that at least $\frac{1}{4}$ inch of the lower end is submerged in the urine and held there for five to ten seconds, after which it is removed, laid on white absorbent paper, and at the yellow or brown transverse line which is usually present, drops of Fouchet reagent are added. A green color denotes the presence of bilirubin, which color varies in intensity according to the concentration of bilirubin. By comparison with a color chart copied from known concentrations, a semiquantitative analysis can be made.

The Anti-Vitamins**

By RUTH WOODS

Nearly half of the last century was spent by scientists all over the world anxiously seeking the cause of a dread disease which frequently killed off entire populations. The disease was pellagra — literally "rough skin," so named because of one of its major early symptoms. Those who survived it were described as "pitiable half-mad wrecks of humanity."

The years spent in tracking down the cause of pellagra were marked by bitter and violent quarrels among scientists and even among political groups. The controversy centered on this question: Was a germ or a poison in food the cause of the disease, or was it the *absence* of something vital in food? The concept of a "deficiency disease" had not yet been fully evolved; Pasteur's germ theory was still excitingly new. So, it is understandable that the idea of a *negative* cause of a disease was extremely difficult to grasp.

The spectacular studies of Goldberger finally demonstrated that pellagra was indeed a "deficiency disease." Soon afterward the deficient food ingredient was found to be nicotinic acid, a new vitamin. The chapter on pellagra was closed; the "poison in corn" theory shamefully discredited. But not for long! One puzzling fact still remained. People in corn-growing regions were dying of pellagra—even with nicotinic acid in their food! Other people, whose food contained less nicotinic acid but who were not forced to subsist mainly on corn, were surprisingly free of pellagra. Something was seriously amiss in this situation. Not until six years ago was the mystery solved.

Strangely enough it was research in an entirely new field—chemotherapy—which provided a means of reconciling the puzzling discrepancies in the pellagra picture. The "deficiency" nature of pellagra was upheld, but so in a way was the

corn "toxin" theory: The existence of anti-vitamins had been discovered.

The discovery of the anti-vitamins (also anti-hormones and other anti-metabolites) is of considerable significance. First it has brought to light a new concept—the fact that *certain compounds almost identical in structure with various essential metabolites are able to induce in animals many of the deficiency signs associated with a lack of these metabolites*. Second, investigation into the mechanism of this antagonistic behavior has provided a new tool for understanding important biological actions and may eventually lead to a clearer understanding of how vitamins* work in the body. Third, the discovery of anti-vitamins has practical applications in therapy as well as in nutrition research. Fourth, the dietary importance of certain foods may require re-evaluation because of their possible anti-vitamin content.

Evolution of the Anti-Vitamin Concepts

The story of the anti-vitamins does not go back to a single piece of research for its beginning. Rather, it has been pieced together like a jig-saw puzzle from clues scattered over many years in extremely divergent fields of scientific investigation. The pellagra mystery provided one of these clues; the discovery of a dramatic new therapeutic agent, sulfanilamide, provided another. An examination of these clues and of how they were integrated to form a single new concept constitutes an exciting chapter in the annals of science.

Following the identification of nicotinic acid as the pellagra-preventive factor in 1937 by Elvehjem, Madden, Strong and Woolley (1), these investigators tested a series of chemicals related to nicotinic acid for their relative vitamin potencies. In this way it was hoped that some basis might be acquired for deter-

mining the relationship between structure and vitamin activity (2). One of these related chemicals, 3-acetylpyridine, was found to have no vitamin activity, but amazingly it was shown to be actually poisonous to nicotinic acid-deficient animals. Normal animals were unharmed by the compound. There seemed to be no explanation for the peculiar behavior of this compound at the time.

Then in 1940, D. D. Woods (3) demonstrated the surprising fact that the power of the sulfonamides to interfere with bacterial growth could be completely overcome by adding a structurally related microbial growth factor, p-aminobenzoic acid, to the bacterial culture media. Woods' purpose in using p-aminobenzoic acid was, like that of Elvehjem's group, to determine the relative bacteriostatic potencies of structurally related compounds. Again, like the analogue of nicotinic acid, the analogue of sulfanilamide produced a result exactly the reverse of what was expected. The theory was set forth that sulfanilamide owed its bacteriostatic activity to the fact that it prevented bacteria from using the essential growth factor, p-aminobenzoic acid.

Conversely, providing extra p-aminobenzoic acid to bacteria which had been paralyzed by sulfonamide enabled these disease-producing microorganisms to resume their normal growth. This competitive action between the sulfa drug and the microbial growth factor was believed to be possible because of the closely related structures of the two compounds.

Theories similar to this had been suggested before with respect to other groups of related compounds, but little attention had been paid to them. When the peculiar competitive behavior between metabolites and structurally related compounds turned out to be involved in the story of the newly discovered "miracle" drugs, the sulfonamides, a

*Reprinted from Borden's Review of Nutrition Research, Vol. VII, No. 8, October, 1946.

lively interest in the phenomenon sprang up. The possibility presented itself that new anti-bacterial drugs might be almost "custom-tailored" by creating compounds similar in structure, but antagonistic in action, to the various growth factors essential for disease microbes.

Anti-Vitamins as Chemotherapeutic Agents

Some real successes along these lines were soon reported. A year after Woods' work with sulfanilamide and p-aminobenzoic acid, Fildes (4) demonstrated that a simple alteration of the tryptophane molecule to yield indole acrylic acid resulted in the production of an antibacterial agent. In the meantime, coincident with the earlier work on p-aminobenzoic acid, McIlwain (5) made another interesting discovery. He found that the same structural change involved in transforming the nutrient p-aminobenzoic acid to sulfanilamide, if applied to the nutrient nicotinic acid, would produce another bacteriostatic agent, pyridine-3-sulfonic acid. In each case, the carboxyl group (COOH) of the original nutrient had been replaced by a sulfonic acid (SO_3H) or amide (SO_2NH_2) group. Snell (6) provided still another example of two competitive, mutually inhibiting compounds by using this same procedure to replace the carboxyl group of pantothenic acid with sulfonic acid, thereby producing thiopanic acid.

It is interesting to note that this type of structural change in the vitamin molecule produces an anti-vitamin which causes deficiency symptoms in bacteria (i.e. growth inhibition) but not in the higher animals*. Therefore, this type of anti-vitamin has been found useful in treating infectious diseases—the antagonistic effects are exerted on the disease-producing microorganisms without disturbing the normal metabolism of the host animal.

Still other inhibitory analogues of these three vitamins may be produced by substituting a ketone grouping ($-\text{COR}$) for the carboxyl

group (COOH), yielding anti-metabolites, aminoacetophenone, 3-acetylpyridine and phenylpantothenone, for p-aminobenzoic acid, nicotinic acid and pantothenic acid, respectively.

Anti-Vitamins in Animals:

Although the sulfonamides had provided a starting point for the new field of anti-metabolites, research workers soon began to wonder whether the scope of such antagonists might not exceed the realm of microbes and extend into the domain of higher organisms. The search for animal anti-vitamins was on. True to expectations a series of compounds was soon discovered which were capable of calling forth in animals the signs characteristically associated with specific vitamin deficiencies.

Before looking into the provocative question as to why scientists should want to produce the very deficiencies they have spent lifetimes on preventing and curing, it might be interesting to first examine the results of these strange efforts.

Thiamine and Pyriethamine: Among the first of the animal anti-vitamins to be created was pyriethamine, prepared in 1943 by Woolley and White (7). As its name indicates, this compound antagonizes the action of thiamine. When fed to mice pyriethamine, a pyridine analogue of the vitamin, produces typical deficiency signs within a few days. The animals become unable to stand upright on their hind legs, toppling over backward when attempting to do so. They rapidly become overly irritable, lose their appetites and finally fall into convulsions, either without any provocation at all or especially when picked up by the tail. Other more serious signs of progressive thiamine deficiency appear, leading eventually to death. Woolley et al found that increasing the amount of thiamine in the diet protected the animals from the effects of pyriethamine. Furthermore, when the animals once had developed thiamine deficiency symptoms due to the administration of pyriethamine, it was possible to cure them, even

in the terminal stages of the disease, by administering thiamine. Woolley and White (8) made the additional interesting observation that pyriethamine is also an active anti-bacterial agent and that its effects can be counteracted by increasing the supply of thiamine in the culture medium.

An important observation in the behavior of pyriethamine is the fact that the action of this compound does not depend upon the absolute amount present, but rather on the dietary ratio of pyriethamine to thiamine. This indicates that both pyriethamine and thiamine compete with each other for the attention of the organism, the one which exceeds quantitatively, winning out. This competitive behavior is believed to be almost universal between the various metabolites and their inhibitory structural analogues.

Following the studies with pyriethamine, analogues of other vitamins were produced which were found to cause diseases characteristic of those occurring with a deficiency of the related vitamin. These diseases were believed to be really deficiencies not only because they presented similar symptoms and disturbances, but also because they were prevented or cured by adequate amounts of the vitamins concerned.

Ascorbic Acid and Glucoascorbic Acid: Experiments with the inhibitory analogue of vitamin C were particularly remarkable because the subjects of the tests, mice, have never been known to develop scurvy. Mice do not need a dietary supply of ascorbic acid, apparently meeting their requirements for this vitamin by internal synthesis. Consequently a scorbutic mouse had never been seen until glucoascorbic acid was fed to a group of these animals (9). Every one of these soon came down with many of the signs of scurvy as usually seen in guinea pigs or other animals susceptible to the disease. What had occurred was obviously a competitive struggle between the internally synthesized vitamin and glucoascorbic acid for supremacy in the biological system. As was expected, glucoascorbic acid

*This applies, of course, to enzymes, hormones, protein derivatives and other important metabolites as well.

of course also precipitated symptoms of scurvy in those animals who ordinarily require vitamin C in the diet. In these animals, the deficiency was promptly corrected by ascorbic acid (9).

Other B Vitamins and Inhibitors: Continued studies have established an antagonistic relationship between riboflavin and any one of three structurally related compounds (10). Nicotinic acid deficiency, like scurvy, never encountered in mice, was induced by feeding 3-acetylpyridine (11), recalling and explaining the first experiments with this compound. It is interesting to note that another nicotinic acid analogue, 3-pyridine-sulfonic acid, is fatal to nicotinic-acid deficient dogs, harmless to normal dogs and ineffective in mice. Phenylpantothenone as well as thiopanic acid, both previously mentioned, compete with pantothenic acid; desthiobiotin with biotin, and so on.

Vitamin K, Vitamin E and Inhibitors: Dicoumarol, first discovered as the injurious constituent of spoiled sweet clover hay causing vitamin K deficiency in cattle (12), was only in retrospect discovered to be an analogue of vitamin K. Similarly, 2,4-dichloro-naphthoquinone, a powerful fungicide developed empirically during the war (13), was later recognized as an analogue of vitamin K. As might have been predicted, the microbial growth-inhibiting powers of this compound were reversed when vitamin K was provided (14). Strangely related to both vitamin K (which is 2-methyl-1,4-naphthoquinone) and to vitamin E (which is α -tocopherol) is the compound α -tocopherol quinone. This compound produces signs of vitamin E deficiency in rats and mice, but its effects are counteracted by vitamin K instead of vitamin E! (15).

Significance of Anti-Vitamins:

As Therapeutic Agents: We may now go back to the question: Why produce vitamin antagonists? Or, for that matter, anti-hormones, anti-amino acids and the like? As has already been mentioned, because the phenomenon of competitive antag-

onism was first popularized by the sulfonamide-p-amino-benzoic acid relationship, the belief arose that other chemotherapeutic agents might be developed against infectious diseases by producing analogues of metabolites. Some of these have already been discussed. It is interesting to note that the most practical of these, 2,4-dichloronaphthoquinone, was not recognized as a competitive analogue of vitamin K until after it had been developed by other standards. The sulfonic acid analogue of pantothenic acid, thiopanic acid, was shown to be capable of protecting rats from streptococcal infection (16). But its action is too weak for it to be of practical therapeutic importance. However, the possibility of finding useful therapeutic agents by this means is increasing with continued research.

Recent reports (17) have described some highly interesting experiments designed to develop an inhibitory analogue useful against infection by certain intracellular micro-organisms. At present there are no therapeutic means of control for such micro-organisms as there are for bacteria. Thus while streptococcal or pneumococcal infections may yield to penicillin or the sulfonamides, there are no effective agents for poliomyelitis or influenza.

Although no such agent for these two diseases has yet been found, Woolley's group has reported a substance which will work against intra-cellular parasites. This is phenyl pantothenone, an inhibitory structural analogue of pantothenic acid. It has been found to be an active antimalarial agent. Phenyl pantothenone is about as active as quinine, while some of its derivatives are even more active. Since much of this work still remains shrouded under military secrecy, there are few details available at present concerning this fascinating development beyond the fact that this compound was originally tested because of observations indicating the importance of pantothenic acid in parasite metabolism.

The applications of anti-metabolites may lead to still other types

of therapeutic agents besides those used to combat infectious agents. For example, it is quite possible that, under certain circumstances, it may become desirable to produce for therapeutic purposes symptoms of a vitamin or hormone deficiency. Why deliberately produce a deficiency state when everyone is trying to prevent this with vitamin pills and hormone injections? Woolley cites two interesting answers to this question:

First is the well-known story of dicoumarol. This compound was found to produce hemorrhages characteristic of vitamin K deficiency (18). At first, dicoumarol was the bane of the farmer's existence, leading to disastrous consequences for the cattle which fed upon the spoiled sweet clover hay containing it. When it was discovered that vitamin K would cure the animals of the symptoms induced by dicoumarol, the realization also came that the two compounds are structural analogues. Dicoumarol is now used clinically before operations in order to prevent dangerous blood clots from forming.

Knowing both the effects of vitamins and of their absence on bodily function provides potentially a spectacular means of controlling at will physiological responses by administering vitamins (as is now done), or their structurally related inhibitors.

With this precept in mind, Woolley (19) set out to produce a selective pharmacological agent which would cause a response the nature of which could be predicted even before the compound was synthesized and which had never before been caused by any known drug.

The metabolite selected for this experiment was tocopherol, vitamin E. It was chosen because in mice a deficiency of this vitamin causes a highly specific response only in the pregnant individual. It is not fatal to the mother animal and is without effect on the non-pregnant female mouse. Vitamin E deficiency in the pregnant mouse causes a resorption of the embryo during the latter part of gestation. This terminates the pregnancy and re-

moves all traces of the embryo. A successful antagonist of tocopherol would, therefore, be expected to produce such a resorptive interruption of pregnancy in mice. Just such an analogue was found in a-tocopherol quinone (19). Curiously enough, this compound is related both to vitamin E and to vitamin K. When a-tocopherol quinone was fed to pregnant mice the desired pharmacological effect—termination of pregnancy—was obtained. Perhaps the strangest part of the experiment was the fact that although the effect obtained was characteristic of vitamin E deficiency, vitamin K and not vitamin E was the only means of reversing the action of this compound. This study although not clinically practical because of the tremendous doses of a-tocopherol quinone required, serves, however, as an experimental model to point the way to new and useful avenues of attack in the employment of structural anti-vitamins.

As Food Factors: Anti-vitamins may occur naturally in certain foods. This brings up the problem that certain foods may actually nullify the vitamin content of other foods and lead to an over-all increase in the vitamin intake requirement.

As an important example of this, we refer again to the history of pellagra. By 1937, nicotinic acid had been clearly established as the pellagra-preventive vitamin. Nevertheless, the "corn-toxin" theory could not be completely discarded, particularly in the face of new evidence from India where pellagra is an urgent problem. From that country Aykroyd and Swaminathan (20) reported that people whose diets contained corn and also supplied 15 milligrams of nicotinic acid per day were succumbing to pellagra. However, other persons receiving only 5 milligrams of nicotinic acid per day in a corn-free diet never developed the disease!*

That these observations were no mere accident was shown when, five years later, investigators in this country (21) were able to inhibit the growth of rats by feeding them corn. Normal growth was resumed

as soon as extra nicotinic acid was provided. A suggestion was made that interference with intestinal vitamin synthesis might be the cause, but there was no evidence to support the theory.

What seems at last to be the real explanation of the mystery was described by Woolley (22) only a few months ago. Recalling the early studies with 3-acetylpyridine as a cause of pellagra in mice (2), he suggested that "corn contains a structural analogue of nicotinic acid which acts as a *positive* etiologic factor in pellagra." In support of this theory it was next demonstrated that such a substance could be extracted from corn and that, when fed to mice, it would cause pellagra. The effect of this as yet unidentified corn extract** is counteracted by nicotinic acid. According to Woolley:

Pellagra is a deficiency disease which results partly from a lack of sufficient nicotinic acid, but more especially from the action of an antagonistic agent in corn which competes with nicotinic acid and thereby intensifies the deficiency." (17).

Theoretical Considerations:

The theory of competitive inhibition of compounds by their structural analogues is not only a relatively new one, but it is still largely in the formative stage. While most of the mechanics of pure chemistry and enzymology which are involved in structural antagonisms are beyond the scope of this paper, it seems desirable from the point of view of clarity and completeness to highlight a few of these theoretical principles.

What is Competitive Inhibition?

It has already been pointed out that the antagonistic behavior of structurally similar compounds is usually the result of such compounds competing for the attention of the organism. The most likely theory to date—but one which is not entirely free of flaws or exceptions—states that the analogue competes with the vitamin for a specific site in an enzyme (23, 24, 3, 25). Either compound can occupy this site at the expense of the other since both, be-

ing closely alike in structure, can react with the chemical groups of the enzyme. If the vitamin combines with the enzyme group, the compound formed passes normally through the metabolic reactions for which the system is adapted. If the analogue of the vitamin combines with the enzyme group, a foreign compound is formed which does not fit into the biological scheme and is therefore valueless to the body.

In this way, the analogue prevents the body from making use of the vitamin-enzyme system, thereby calling forth the same symptoms as would occur in an actual deficiency of the vitamin. Whether the vitamin or its analogue combines with the enzyme depends on the relative concentrations of the two. Thus, it is not the presence of the analogue *per se* which will inhibit the action of the corresponding vitamin, but rather the ratio of analogue to vitamin which will determine the course of action.

The phenomenon of competitive inhibition has a number of interesting phases. For example, the action of inhibitory analogues varies with the animal species tested being inhibitory in some and not in others. Also, in some cases the related vitamin will not reverse the action of the inhibitor. Again, in some species, the analogue will be inhibitory only if the corresponding vitamin is a nutritive essential for the particular species. In other animals, no such correlation exists.

A final point of interest is the fact that antagonisms of a non-competitive type have also been brought to light. These antagonisms have nothing to do with structural similarities between the compounds involved and present an entirely different subject in themselves. In this class of antagonisms the inhibitors are generally proteins or amino acids which work by directly inactivating the vitamins (or other metabolites) involved. Examples of these include ascorbic acid oxidase which destroys ascorbic acid by hastening its oxidation; avidin, the

*The recommended daily allowance for nicotinic acid is from 15 to 18 mgs.

**Apparently a pyridine compound.

mysterious constituent of egg white, which combines with biotin thereby rendering it unavailable; and an unidentified enzyme in raw fish which destroys thiamine by splitting it into fragments which the body cannot make use of. Two other interesting examples are the reversal of the action of acetylpyridine (the anti-nicotinic acid analogue) by the amino acid tryptophane, and the reversal of the action of the sulfona-

mides (anti-p-aminobenzoic acid analogue) by the amino acid methionine.

Conclusion:

The discovery of the anti-vitamins marks a new chapter in the history of nutrition research. The early study of vitamins established the principle that certain compounds present in trace quantities in the diet had vital *positive* biological func-

tions. The studies outlined in this *Review* have now shown that other compounds may have equal significance in a *negative* direction. These latter compounds exert their effects by interfering with the action of the vitamins themselves. This means that from the point of view of nutrition, one must not think in terms of *absolute* vitamin intake or requirements, but in terms of *net* vitamin availability.

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News Notes

February 1, 1947, Deadline for Veterans on Easy G. I. Insurance Reinstatement

The deadline established by the Insurance Act of 1946 for most veterans to take advantage of the easy reinstatement of their G. I. Term Insurance is February 1, 1947, six months after passage of the Act, according to a folder entitled: "G. I. Insurance Streamlined" published by the Illinois Commercial Men's Association.

In the Insurance Act of 1946 passed in its closing sessions, Congress met every major reason why

many veterans dropped their National Service Life Insurance after leaving the service. These changes and an explanation of how to get the most out of G. I. Insurance are described fully and clearly in the folder, "G. I. Insurance." The folder, published primarily for veteran members of the Illinois Commercial Men's Association, is available free to other interested veterans. Veterans desiring free copies should send a request to R. A. Cavanaugh, c/o of I. C. M. A., 332 S. Michigan Avenue, Chicago 90, Illinois.

Major reasons for dropping G. I. Insurance have been lack of lump sum payment to beneficiaries, restricting of beneficiaries to members of immediate family, and omission of endorsement plans among permanent plans offered. All these, important to civilian needs of veterans, have now been changed. Congress added a disability income provision to pay \$50.00 a month insurance income in case of total disability occurring any time before age 60.

"Not a single one of your reasons remain as excuses for neglecting

your service insurance today," the folder states, "so far-reaching and drastic are the changes just made." All of the changes are then explained in non-legal, easily understood language. Millions of veterans will now reinstate their insurance, it is predicted. However, to reinstate the term insurance easily without medical exam, as most veterans will want to do, it is necessary to act before February 1, 1947. For six months from passage of the law, reinstatement is made easy for the average policy, a term policy. Only two premiums need be paid and no medical examination taken. Thus, at present, no matter how long the insurance has lapsed it can be reinstated without a medical exam. After February 1, 1947, a medical exam will again be required if the insurance has lapsed more than six months.

Veterans who never had G.I. insurance can now make original application for it even though they are out of the service, "G.I. Insurance Streamlined" explains. The folder is a valuable help to veterans who know that one sure way of getting the most security out of their service careers is to "Keep your G.I. Insurance . . . now, and for the rest of your life."

Under the heading of "What Should You Do About Converting," the folder says: "If your term insurance was taken out on or before December 31, 1945, you can keep it 8 years. (Term policies originally applied for on and after January 1, 1946, can be kept only 5 years.) Term insurance gives you the maximum protection at the least initial cash outlay. It was given so that you could have the greatest insurance during your and Uncle Sam's emergency — World War II. Consider that your emergency continues until you are well re-established in civil life.

"The best thing to do," advises the pamphlet, "is to keep the term insurance until you know how much you can afford to convert. Suppose you are back on the job now; it is steady. You know how much money you need for other reconversion plans: wife, home, car, refrigerator, children. Then think about converting. If a home, wife and chil-

dren are in or coming into the picture, you owe them the full \$10,000 protection. Convert \$5,000 if you want, but continue the other \$5,000 as term insurance. At the end of eight years of the term policy your income may have increased, you will be more convinced of the value of this insurance, and you may be able to convert more to a permanent plan. Or, if Congress makes the term policy renewable as it did after World War I, you can then renew your term insurance at your attained age. In that way you may be able to carry a full \$10,000 protection as part permanent plan and part renewable term insurance.

"Also, by keeping the balance as term, you can carry the greatest of the extra disability insurance: \$25.00 in the example above on your permanent policy, and \$25.00 on your term totaling monthly disability payments of \$50.00."

In "G.I. Insurance Streamlined," the legal phraseology of The Insurance Act of 1946, Public Law No. 589, is unraveled and the changes are conveniently grouped under such headings as: how your term insurance is changed, how do changes affect conversion, what should you do about converting, changes of permanent plans, and others. Also given are many hitherto unpublished facts and tips about government insurance.

Fourth Annual Medical and Surgical Symposium Sponsored by Watts Hospital Staff of Watts Hospital, Durham, N. C.

Wednesday, February 12, 1947.
11:00 A. M.: Clinico-Pathological Conference, presented by Sidney Farber, M. D., Department of Pathology, Harvard Medical School, Boston, Mass., and Charles D. May, M. D., Associate in Pediatrics, Harvard Medical School, Boston, Mass.

2:30 P. M.: "Surgical Aspects of Diabetes," Leland S. McKittrick, M. D., Boston, Mass.

3:30 P. M.: "Recent Advances in the Study and Treatment of Diabetes," Howard F. Root, M. D., Boston, Mass.

8:00 P. M.: "Viral Hepatitis," Joseph Stokes, Jr., M. D., Professor of Pediatrics, University of Penn-

sylvania Medical School, Philadelphia, Pa.

9:00 P. M.: "Pericardial Scars," Francis C. Wood, M. D., Assistant Professor of Medicine, University of Pennsylvania Medical School, Philadelphia, Pa.

Thursday, February 13, 1947.
11:00 A. M.: Clinico-Pathological Conference, presented by J. E. Ash, Colonel, Medical Corps, Director Army Institute of Pathology, Washington, D. C., and Wallace Yater, M. D., Former Professor of Medicine at Georgetown University.

2:30 P. M.: "Some Clinical and Physiologic Aspects of Portal Cirrhosis," Albert M. Snell, M. D., Mayo Clinic, Rochester, Minn.

3:30 P. M.: "The Current Status of Calcium Penicillin in Beeswax and Peanut Oil," Monroe J. Romansky, M. D., George Washington University School of Medicine, Washington, D. C.

8:00 P. M.: "The Present Status of Effective Specific Therapy Based on Exact Hematologic Diagnosis," Charles A. Doan, M. D., Dean, College of Medicine, Ohio State University, Columbus, Ohio.

Squibb Reports First-Quarter Earnings Increased to 47 Cents Per Share From 42 Cents a Year Ago

Declares Dividend of 25 Cents on Common Stock

Stockholders, at Annual Meeting, Re-elect All Directors; John N.

Staples Retires as Senior Vice-President

Consolidated net earnings of E. R. Squibb & Sons and wholly owned subsidiaries in the western hemisphere for the first quarter ended September 30, 1946, was \$858,408 compared with \$781,984 for the corresponding quarter a year ago, Lowell P. Weicker, president, announced today (Thursday) at the annual stockholders' meeting. This was equal to 47 cents per share on the 1,514,694 shares of common stock outstanding, after providing for taxes on income and preferred dividends, compared with earnings of 42 cents per common share on the stock outstanding a year ago after adjusting to a three-for-one basis in accordance with the recap-

italization in December, 1945.

Provision for United States and foreign income taxes was \$649,252 for the 1946 quarter compared with \$755,137 for the like quarter last year. Net income before provision for such taxes was \$1,507,660 for the quarter just closed compared with \$1,537,121 for the corresponding quarter last year.

The stockholders re-elected all of the company's present directors. At a meeting of the board of directors following this, all of the company's officers were re-elected with the exception of John N. Staples, who retired as senior vice-president. Mr. Staples will continue, however, as a director of the company.

Directors of E. R. Squibb & sons today (Thursday) declared a dividend of 25 cents per share on the common stock, payable December 12, 1946, to stockholders of record at the close of business November 27, 1946. A dividend of \$1 per share was declared on the 4 percent cumulative preferred stock, payable February 1, 1947, to stockholders of record at the close of business on January 15, 1947.

In acting for our clients we receive compensation for our services either directly or indirectly, through the placing of advertising, and are ready to disclose this information on request. Doremus & Company, New York.

Things You Should Know About Your New Peacetime Army

In order to raise and maintain on a volunteer basis the Army of 1,070,000 men estimated by the War Department as needed by July 1, 1947, it will be necessary to recruit an average of 40,000 men a month.

The U. S. Regular Army offers volunteer training in many skills and trades, ranging from aviation mechanics to cooking and welding.

The Army Medical School in combination with the Army Institute of Pathology, Washington, D. C., has one of the largest and most complete collections of equipment and material illustrating all phases of clinical and pathological laboratory examinations.

The Army's "navy" includes sev-

eral hundred ships ranging from transports to ferry boats. The Army also operates its own railroads, including the 45-mile line at Aberdeen Proving Ground, and the 30-mile line across the Panama Canal Zone.

The American soldier might be called "the healthiest man in the world." The Army provides 13 doctors and 12 nurses for every 2,000 troops, with the finest medical equipment and hospital facilities. In World War I, deaths and disease totaled 156 in 10,000; in World War II, only six in 10,000. In peacetime, 5 per cent of the Army's total enlisted strength is engaged in safeguarding the soldier's health.

Food inspectors of the Veterinary Corps, in 1945 alone, checked 8,271,175,085 pounds of food of animal origin purchased for the service, rejecting 246,349,652 pounds as unsatisfactory.

Fort Knox, Ky., is known as the U. S. Treasury's gold depository. It also is one of four great training centers for the peacetime Regular Army. The fort's 106,000 acres has 3 hospitals, 17 chapels, 9 movies and an 18-hole golf course — as well as barracks, dormitories, guest houses and a 1,000-family unit housing project.

New pay scales increase enlisted men's pay from 50 per cent (for privates) to 19 per cent (for technical sergeants). It is estimated that, with hidden pay for free items, the average private has a take-home pay that equals or exceeds that of the average civilian worker.

The Army's retirement program permits a man to retire with one-half pay after 20 years' service or three-fourths pay after 30 years. Thus a master sergeant would get a monthly income of \$107.25 (at the end of 20 years' service); or \$185.63 (at the end of thirty years' service).

Army Engineers have a three-and-a-half billion dollar backlog of public work which piled up during the war. Congress has appropriated for their peacetime work sufficient funds for nearly 500 river and harbor projects and 175 flood control programs, as well as for needed surveys and advance plans for other essential projects.

FEDERAL SECURITY AGENCY U. S. Public Health Service

Dr. Thomas Parran, Surgeon General of the United States Public Health Service Federal Security Agency, announces that approximately 120 one-year fellowships in medical research are open to men and women who are graduate science students. These fellowships are part of the program of the National Institute of Health, a unit of the Public Health Service.

A war-created void in scientific manpower offers unlimited opportunity to trained personnel in the public health field. Dr. Parran pointed out. He declared it would take five years or longer to make up the shortage of scientists.

The National Cancer Institute, which operates as a division of the National Institute of Health, also has funds to train approximately 30 physicians in the diagnosis and treatment of cancer, the Surgeon General said. Under a federally financed program, doctors wishing to specialize in this field may be appointed as trainees and be assigned to authorized non-federal, non-profit institutions in various parts of the country.

The National Institute of Health offers research fellowships to graduates of accredited colleges who have majored in such subjects as biology, chemistry, dentistry, entomology, medicine, physics, and other scientific fields.

Paying a yearly stipend of \$3,000, Senior Research Fellowships are awarded to men and women who hold Ph. D. degrees in one of the specified scientific subjects. Junior Fellows, who receive \$2,400 annually, must hold a master's degree in science, or must have completed the equivalent of a master's degree in postgraduate study. Fellowships are for one year from the date of award, and may be renewed for a second year.

Applications for fellowships and traineeships should be sent to the Director, National Institute of Health, Bethesda, Maryland.

The Public Health Service also administers fellowships awarded by the State Department to health personnel from other American republics and the Philippine Islands. Be-

The Geography of Salmonella

By

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THERE ARE approximately 150 types of *Salmonella* known to date. While not many of these strains have acquired great epidemiologic importance in all parts of the world, in a single case or outbreak selected by random sampling, any *Salmonella* type may be encountered.

Only a few types of *Salmonella* occur exclusively in man. The great majority of the strains cause primarily infestation in animals and birds. Such animal infections attain great importance in human medicine when transferred by food, as meat and eggs, to man.

Finally, the clinical picture of salmonellosis in man is not a single clinical entity but a series of syndromes.

As a result of the studies of American authors, particularly Hormaeche et al. (1), Bornstein (2) and Seligmann et al. (3), the "Doctrine of Montevideo" has been accepted. According to this theory, the reaction of the infected person depends upon his age and general health, while the type or strain of *Salmonella* plays a less important role. Thus children and young animals, old and sick people are more prone to develop septicemic forms or meningitis, while healthy and mature individuals show only moderate generalized symptoms. Any *Salmonella* may, therefore, produce the following clinical syndromes of salmonellosis:

1. *Salmonella* fever, the "paratyphoid disease" of older authors.
2. *Salmonella* septicemia, with irregular fever and often lethal outcome.
3. *Salmonella* enteritis, either choleraform (rare in adults), or dysentery-like.
4. Localized inflammation, as pseudoappendicitis, cholecystitis, salpyngitis, pleuritis, etc.
5. Symptomless carrier state.

There are, however, a few *Salmonella* strains which predominate as causes of one or another form of salmonellosis. The paratyphus bacilli A, B and C, and *S. sendai* are often isolated from *Salmonella* fever. *S. cholerae-suis* frequently evokes septicemia. Members of the group "E" in America cause enteritis rather than other disease. On the other hand, the very frequent *S. typhi-murium*, *S. newport*, *S. oranienburg*, *S. panama* and *S. montevideo* do not show much preference for any particular type of salmonellosis.

When the problem of prevention of salmonellosis is considered in its entirety, two questions arise:

First, how is salmonellosis being spread?

Second, which strains of the 150 known types are the most important?

The answer to the first question is not easy. Felsenfeld (4) enumerated the following sources of human *Salmonella* infections: human carriers and cases, meat and fowl, foods as creamy pastries, pies, ice cream, mayonnaise and eggs; mechanical vectors such as flies and other insects; polluted water and fomites; even cows, horses, foxes, dogs, rats and other animals.

The answer to the second question depends to a large extent on detailed responses to the first; the hygienic habits and supervision of human and animal carriers; the quality and cleanliness of the food, the diseases prevalent among animals and birds utilized by the people as food and the amount of infestation of rodents which have access to stored food. While the investigation of the modes of infection is being discussed elsewhere, the task of this communication is to analyze to what extent the local habits and customs influence the distribution of *Salmonellae*.

It is unfortunate that data are not available from all countries and states.

Little attention is paid to *Salmonellae* in many places. With the exception of lists published by *Salmonella* centers, only few data can be obtained. Even in a country as *Salmonella*-conscious as the United States, 13 states still do not type or send to a typing center *Salmonellae* isolated in their laboratories but are satisfied with the general diagnosis of "paratyphoid bacillus." Excellent information is at hand from the other states of the U. S. A., from Canada, Mexico, Uruguay, Denmark, England, Hungary, South Africa, and Netherlands Indies (from the last only before the Japanese occupation). Numerous helpful statistics were published by U. S. Army personnel from the Mediterranean Theater of Operations, New Guinea and Panama. Much material is available from Cuba, Panama, Venezuela, Brazil, Argentina, Norway, Sweden, Germany, Czechoslovakia, Palestine, India and Australia, thus permitting the sketching of a picture of the geographic distribution of the most important types.

Rare strains, which occur in less than one per cent of the epidemics, are not considered in this paper.

The isolation of one or another of the less usual types in different localities is often described in current literature. The writers of this article feel that there is still not enough material on hand to warrant definite statements concerning the distribution of such organisms. Neither is *E. typhosa* (considered a *Salmonella* because of its serologic behavior) discussed in this paper, because of the somewhat different epidemiology of typhoid fever. Finally, *S. pullorum* and *S. gallinarum*, very important in veterinary medicine but rarely found in human pathology, are not included in

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this study. As a result of this limitation the number of strains which have to be considered here is reduced to fourteen.

These *Salmonellae* are enumerated here in the order which they follow in the serologic scheme of White-Kauffmann.

S. Paratyphi A. This organism is only exceptionally encountered in the Continental United States. One recent outbreak was described in a state hospital (5). It is known, however, that epidemics in mental institutions do not necessarily reflect the epidemiologic status of the general population. One carrier of an unusual strain may cause an outbreak in a closed institution. The large statistics of Edwards and Bruner (6), Seligmann et al. (3) and Rubinstein et al. (7) as well as the data of numerous less extensive reports confirm that *S. paratyphi A* is very unusual in the northern half of the United States. In the South, this organism was reported from Florida (8) and from Georgia (9), i. e., from states with a warm and moist climate.

S. paratyphi A was recently isolated in the Mediterranean area in laboratories of the U. S. Army (10), in Palestine (11) and in Vienna (12). It caused a larger outbreak among German soldiers in Austria. A certain number of strains was constantly found in Germany (13). It is also present in Czechoslovakia (14). It comprises about 8 per cent of all *Salmonella* infections in India (15) and is very frequent in the Netherlands Indies and in Africa. Among 32 *Salmonella* cultures from different human sources received from the Philippines, we found 4 *S. paratyphi* strains, while this type was not present among 207 other *Salmonella* cultures received from N. American laboratories. Even a case of *S. paratyphi A* infection in a cat was described in Argentina (16). A great number of such organisms were isolated from rats (17). Thus the infection can be propagated not only from man to man but also from rodents to man.

It may be safely stated that *S. paratyphi A* predominates in subtropical and tropical regions. It is very rarely found under the moderate climate of the more northern part of the United States. It is, however, present in Continental Europe.

S. Paratyphi B (*S. schottmuelleri*). This organism is constantly reported in the United States of America, where it causes about 20 per cent of all salmonellosis cases (4). The incidence of *S. paratyphi B* is lower in the New England States (3, 7), and higher in the Central States and in the South (9). It is very frequent in South America (1), in the Mediterranean area (10, 11), predominates in Germany (13, 18) (about 40% of all *Salmonella* infections) (15); causes frequent outbreaks in England (19, 20, 21, 22, 23, 24) (about 10 per cent of all *Salmonella* infections) (15); predominates in Czechoslovakia (14), and is being reported from all other countries. It causes about 8 per cent of the salmonellosis cases in India and 20 per cent in the Netherlands Indies (15). *S. paratyphi B* is frequent in animals. It is being found in rats (17), healthy pigs (25, 26), cows (27), and sheep (28). It is interesting to notice that fowl only rarely

harbor this organism. In the United States, it is nearly exclusively transferred from man to man, most frequently through the activities of food handlers. In South America and in Germany, because of the heavy infestation of farm animals, that source has to be taken into consideration.

S. paratyphi B is an organism found in all parts of the world where a search for it was established. While in the United States it is mostly propagated by human carriers, in other countries animal sources also have to be considered in its epidemiology.

S. Typhi-Murium (*B. aertrycke*, *B. breslau*) is the most common *Salmonella*. Seligmann et al. (3) found it in about 37 and Rubinstein et al. (7) in about 48 per cent of their cases. Kauffmann (14) estimates *S. typhi-murium* infections 60 to 65 per cent of all salmonellosis infections; about 55 per cent in England, 44 per cent in Germany, and 22 per cent in the Netherlands Indies. It is very frequent in all parts of the United States (4, 8, 9, 29, 30, 31), Mexico (32, 33, 34), South America (1, 35, 36), Mediterranean area (10), Denmark (37), England (38), Germany (13), Australia (39) and New Guinea (40). It is frequent in fowl in the United States (41), Britain, Canada (42, 43, 44), South America (45, 46), and Denmark (47, 48). *S. typhi-murium* was found in healthy pigs (26, 49), sick hogs (50, 51), camels (52, 53), cows (28), horses (54, 55), foxes (56, 57), dogs (58), muskrats (59), rats (16, 60, 61, 62). It is interesting to notice that in Mexico (17) 77.6 per cent, in Calcutta (60) 73.4 per cent and in Denmark 64 per cent of the organisms isolated from rats were *S. typhi-murium*, while in Sao Paulo (61) all *Salmonellae* in rats proved to be *S. typhi-murium*.

S. typhi-murium, however, is very rare in human salmonellosis in India (15). In countries where fowl is freely consumed, where food containing custards and other similar egg products are frequently eaten, *S. typhi-murium* infections are necessarily frequent. There seems to be an inter-relationship between fowl and other animals in the exchange of the infection. Hinshaw (63) often found *Salmonellae* in snakes which fed on fowl eggs. Rats frequently contaminate food during storage. *S. typhi-murium* survives for several weeks on food (90). It is, therefore, easy to understand that this omnipresent organism causes so many infections, except in India, where perhaps the special food habits of the Hindus reduce the number of the infections.

We have to accept *S. typhi-murium* as the leading *Salmonella* in most parts of the world. Fortunately most infections with this organism show only gastroenteritis of a few days' duration, resembling "Sonnen dysentery."

S. Derby is found in about 3 per cent of human *Salmonella* infections in the United States (6, 7). Recently it caused an outbreak in a hotel (65), was isolated from children (66), and frequently from fowl (41). *S. derby* was found in market meat (49), normal hogs (67) and sick animals (6). In South America it is often isolated from man (36), pigs (51) and fowl (45). A few cases were observed in the Med-

iterranean (10). Hogs in Germany (68) were reported as infected. This infection is very rare in humans in Europe (13, 15), but frequent in the Netherlands Indies (15). Most human infections with *S. derby* belong to the clinical group of enteritis. The strains which we identified from South America and the United States came from cases of diarrhea.

S. derby seems to infect swine and fowl. Human carriers are very rare. Its main domain is America.

S. Paratyphi C (*S. hirschfeldii*, van Loghem's bacillus) has its home in the Old World. It is practically unknown in America. A case in Cuba was recently described (69). This is, perhaps, the first authentic isolation of this organism in the New World. This type, however, is frequent in Palestine (11), Egypt (70), India (71) and the Netherlands Indies (15). Paratyphoid C bacilli were isolated only from man. The epidemiology of this infection closely resembles that of paratyphoid A; the clinical form being typhoid-like fever.

S. Cholerae-Suis (*S. suipestifer*) shows only slight serological and biochemical differences from *S. paratyphi C*. Infections with this organism are frequent in the United States (3, 7, 9, 31) and in South America (36). *S. cholerae-suis* occurs in about 7 to 9 per cent of all salmonellosis cases in the New World. In Europe and Asia, the infection is less frequent (10, 13, 37). An epidemic in Greece was recently described (72). More cases occurred in England (15). *S. cholerae-suis* is rare in fowl (41, 73) but frequent in swine (25, 51, 67) and occurs also in cattle* (74), dogs (75), foxes (56) and rats (17). Human carriers were never found (2, 3, 4, 64), therefore infection from meat has to be assumed. The disease is of the septicemic type, with a considerable (10 to 25 per cent) mortality, which is higher than the death rate in typhoid and paratyphoid fever. It is the opinion of the writer, therefore, that *S. cholerae-suis* is the most dangerous *Salmonella*.

This organism seems to occur all over the world. Infections, however, are more frequent in America and in the Netherlands Indies (15).

S. Thompson is an organism which belongs to the paratyphoid C group, as *S. cholerae-suis*. It is very rare in America (2, 3, 4, 6, 7, 41, 46), but causes about 10 per cent of salmonellosis in Denmark (15). It seems to be the chief agent in poultry salmonellosis in Britain (76). It may be spread by infected fowl eggs (43). *S. thompson* is not rare in Germany (15). This infection is present in eggs consumed in America (44, 77). If this strain would be propagated on this hemisphere in fowl, human infections with *S. thompson* will become more frequent in this country also.

At present, *S. thompson* is frequent in Europe but rare in America. Because of its frequency in fowl, the transfer to man through eggs seems to be the main route of infection.

S. Montevideo is quite a common agent of human salmonellosis in America (3, 6, 7, 9, 31, 36, 51, 64, 78, 79). It was frequently found in normal hogs in Argentina (26), in healthy chickens in Mexico (45)

and in sick fowl in the Americas (41). It is relatively frequent in the Mediterranean (10) but rare in Denmark (37). While it occurs in 3 to 5 per cent of *Salmonella* infections in North America and its frequency increases to the south of the continent, it is practically never found in Europe.

S. montevideo was often isolated from food poisoning and from human carriers. Both human and animal sources seem to play an equally important role in its propagation. The infection is most frequently encountered in the New World.

S. Oranienburg is serologically different from *S. montevideo* only in parts of its "H" antigen. It occurs in a slightly higher number of cases of human salmonellosis (3, 6, 7, 8, 9, 31, 36, 51) than *S. montevideo*. It is also more frequent in Denmark (37) and Germany (13) but does not attain the importance it has in America. It is frequently found in fowl in America (41) and was found in eggs (44, 80). The epidemiology of *S. oranienburg* seems to be the same as that of *S. montevideo*.

In our material, *S. montevideo* and *S. oranienburg* occurred in about equal numbers. We found them in cultures from the Philippines, Panama, Venezuela and several North American states.

S. Newport occurs in about 9 to 11 per cent of cases in America (3, 7, 31, 33, 36, 81). It recently caused an outbreak in Canada, was isolated in the Mediterranean (10), Palestine (11), occurred in about 8 per cent of *Salmonella* infections in Denmark (15), about 7 per cent in England (15) and about 8 per cent in Germany (13). It is rare in Hungary (82). *S. newport* was isolated from market meat (49), healthy hogs (25), healthy poultry (45, 46), sick fowl (41), eggs (44), foxes (56), snakes feeding on poultry eggs (63), etc. Because the Netherlands Indies showed also 7.7 per cent of the *Salmonella* infections in man caused by this organism, one may suppose that the distribution of *S. newport* over the world does not show considerable fluctuation. It seems to acquire, however, local importance in South America.

S. newport was isolated from all clinical types of salmonellosis. Considering the frequency of this organism in human carriers, animals and birds, it is not surprising that it is readily encountered in diseased persons.

S. Enteritidis occurs in 1 to 3 per cent of human *Salmonella* infections in America (3, 6, 7, 36). It is not frequent in the Mediterranean (10) but is a major cause of food poisoning in the U. S. S. R. (83), Germany (15), Denmark (37) and England (15). About 10 to 15 per cent of human *Salmonella* infections in Europe seem to be due to *S. enteritidis*. This organism is also found in India (15). Up to 5 per cent of the *Salmonellae* in the Netherlands Indies (15), is this organism. It is common in duck eggs in Denmark (47) and Germany (84) and in rats in India (60) and Sweden (62), while in America it is rare in fowl (41), but was reported in calves in tropical parts of the continent (85, 86). The latter, however, could perhaps be the "var. dublin" which is frequent in cattle.

S. enteritidis is an infection prevailing in Old World fowl and, consequently, causing disease mostly among the consumers of eggs and poultry from those parts of the globe.

S. Dublin is an organism practically unknown in North America. It is a frequent incitant of disease in Denmark and India (15), causing there about 3 per cent of all *Salmonella* cases in man. It is a frequent cause of loss of calves in Brazil (87) and South Africa (88). It was recently recovered from cattle in Australia (89). It caused outbreaks of a milk-borne epidemic in South Africa (90), and England (91), where it is endemic in cattle (92). Many human cases occur in Denmark (15, 37) where ducks are infected with this *Salmonella* (47, 77). In Sweden rats were also found to harbor *S. dublin* (62).

A certain degree of confusion in the *S. enteritidis* group cannot be avoided because of the relatively small serologic differences between *S. enteritidis*, *S. dublin*, *S. blegdam* a.o. Even if it is sometimes necessary to read the reports on the occurrence of certain strains with a critical eye, it seems certain that *S. dublin* is a bovine-adapted organism which, perhaps, was transferred from England to South Africa and Australia. The origin of the South American infections is not clear. Further study of European "enteritis-like" strains will elucidate the question why *S. dublin* occurs in ducks only in Denmark when other *Salmonella* infections of this bird show more equal distribution in Denmark and in nearby countries.

Human infections with *S. dublin* are caused by drinking unpasteurized milk from infected cows and transferred from poultry, probably by eggs and meat. The disease has a "spotty" global epidemiology, being frequent in pure cattle raising countries. Infections are absent in the U. S. A.

S. Panama is an organism typical of the New World. It causes 3 to 5 per cent of human *Salmonella* infections in America (2, 3, 4, 6, 7, 9, 36), but is rare in Europe (10, 93). While it was occasionally found in healthy pigs (26), the chief animal source of infection is poultry (6, 41). Human carriers are not infrequent. Out of the 17 *S. panama* strains examined by us, 4 came from symptomless food handlers. This organism may, however, cause any clinical type of salmonellosis.

In America *S. panama* is listed among the more frequent *Salmonellae*, while in other parts of the world it is unknown (15) or very rare. It is found in man as well as in birds, therefore infections both from human sources and from poultry can be expected.

S. Anatum is isolated from 2 to 4 per cent of salmonellosis cases in North America (2, 3, 6, 7, 9). It is somewhat more frequent in South America (36), but considered rare in Hungary (82) and in the Mediterranean area (10). It occurs in Palestine (70). *S. anatum* infections are frequent in Norway and in the Netherlands Indies (15). We found it also among cultures from Panama, Venezuela and the Philippines. *S. anatum* is often present in healthy and sick fowl (41, 45, 46), in market meat (49), in healthy and sick

pigs (25, 26, 51, 67) and even in dogs (94) and foxes (56).

The disease caused in man is usually a simple gastro-enteritis. Human carriers, however, are frequently encountered.

The distribution of this organism is "spotty." While most infections appear in America, an endemic focus seems to be present in Norway. *S. anatum* is frequent in the Pacific region. The infection is carried by man, fowl and swine.

It has to be remembered that some unusual *Salmonella* strains may attain local importance, as *S. melagardis* in the Mediterranean (10), *S. hylitigios* in Germany (95), *S. alamy* in Hungary (96) and *Br. hemia* (97), *S. newington* in a state hospital (6) in the United States, etc. It depends on the public health measures set into action at the occasion of an outbreak if the infection remains isolated and dies out or if it will spread. The physician alone cannot accomplish everything in this field. The co-operation of the public health authorities and the veterinarians is very important because of the frequent animal origin of salmonellosis.

DISCUSSION

The established opinion of many physicians formerly was that the following *Salmonellae* are the most important in human medicine: *S. paratyphi* A and B, *S. typhi-murium* (Breslau bacillus) and *S. enteritidis* (B. gaertneri). The work of *Salmonella* centers all over the world, particularly in America, Denmark and the Netherlands, proved that *Salmonellae* have a certain geographic distribution. While any of the 150 *Salmonella* strains may be discovered during the investigation of a case of sickness or outbreak of an epidemic or food poisoning, the most frequent organisms encountered in the United States are: *S. paratyphi* B, *S. typhi-murium*, *S. cholerae-suis*, *S. montevideo*, *S. oranienburg* and *S. newport*, followed by *S. derby*, *S. enteritidis*, *S. panama* and *S. anatum*. Three more organisms not discussed in this paper are also often isolated: *S. bareilly*, *S. sentenberg* and *S. gize*. These latter do not achieve a geographic importance. The diagnostic methods used for the detection of salmonellosis have to be modified according to the local strains. It is of little value to test the serum of the patient only with *E. typhosa*, *S. paratyphi* A and *S. paratyphi* B antigens. It is also unsatisfactory to test a *Salmonella*-suspicious organism only with *S. paratyphi* A and B, *S. enteritidis* and *S. typhi-murium* antisera and if the culture does not agglutinate, discard it as "non-pathogenic." Fortunately, this does not happen except in rare cases. Most laboratories forward their *Salmonella* strains to a *Salmonella* center, which carries out the typing without fee, as a public service.

The diagnosis of the particular strain involved in the case of disease or outbreak is of paramount importance, because the epidemiologic features of the *Salmonella* type may point to the source of the infection, thus helping to avoid further cases.

The geographic distribution of the *Salmonellae* gains

significance in the recognition of the fact that our greatest hope for the prevention of the spreading of *S. paratyphi* A and C into the colder regions lies in the maintenance of adequate hygienic measures. These organisms occur only in man, therefore the battle against their propagation calls for the same means as are used against the spread of typhoid fever. Greater difficulties are encountered in the checking of *Salmonellae* which are frequently found in animals. The recent transfer of *S. dublin* to Australia is a memento served as a warning hand for those who fight against infections. *Salmonellae* propagated by cattle and swine can be prevented from causing human disease by proper preparation of food. The difficulties in heating the inside of a thicker piece of meat to a temperature sufficient to kill *Salmonellae* which occur also in the best inspected market meat (49) are too well known to be discussed here. Special problems arise in the consideration of fowl and eggs as a source of salmonellosis. Edwards and Bruner (6), and Hinshaw (41) performed considerable investigative work in this field. Hinshaw proved that the distribution of *Salmonella* types in fowl is similar to the occurrence of the respective strains in man. Kessel et al. (98) gave further proof of the relation of human to avian salmonellosis. In countries consuming much fowl and eggs, as in the United States, the answer to the *Salmonella* problem lies not only in the control of human carriers but largely in the eradication of the disease and carrier state in fowl.

Special problems arose following the great movements of men due to the war and the improved overseas transportation. The strict control of food and food handlers, together with vaccination against typhoid, paratyphoid A, B (and C) practiced by the American and British Army not only kept the number of cases to a minimum but also prevented the importation of paratyphoid A and C infections by returning soldiers. In view of the favorable sanitary conditions, even if somebody would be flown to the U. S. A. during the incubation period of salmonellosis caused by a *Salmonella* not domesticated in America, the danger of an outbreak is not larger than if the person carried any well-known type of salmonella. As was stated above, strains propagated from man to man have little chance of spreading in the U. S. A. Greater danger could arise when uncontrolled animals, mainly fowl, would be introduced into the country and spread a new infection among native poultry, thus creating new sources of human salmonellosis.

SUMMARY

The global epidemiology of the most important *Salmonella* strains, i.e., *S. paratyphi* A and B, *S. typhimurium*, *S. derby*, *S. paratyphoid* C, *S. cholerae-suis*, *S. thompson*, *S. montevideo*, *S. oranienberg*, *S. newport*, *S. enteritidis*, *S. dublin*, *S. panama* and *S. anatum* was discussed with special regard to the clinical forms of salmonellosis and modes of propagation.

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A Clinical Consideration of the Malfunctioning Non-Calculus Gall Bladder

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IN 396 CONSECUTIVE cholecystographic studies there were 75 cases in which the only abnormal finding was a sluggish emptying gallbladder. The high incidence of dysfunction of the non-calculus gallbladder without other abnormality, made it desirable to investigate its clinical significance. This condition seemed to be too prevalent to have any real pathologic significance. It is important to note that an incidence of about 10 per cent of sluggish emptying gallbladders is found in routine examinations of individuals who are entirely asymptomatic. In the 396 cases with digestive disorders the incidence doubled. However, it is known that both functional and pathologic gallbladders are compatible with normal health. This functional condition is frequently considered to be due to a diseased gallbladder. Although it is a complex medical problem, it is often treated surgically.

There seems to be no accurate data on the emptying status of the gallbladder to determine precisely when to consider it abnormal. Regardless of the many contributions on the subject of functional changes of the gallbladder, the conception of the etiologic factors involved are not well understood. Because of the lack of specific clinical correlation concerning the non-calculus, sluggish emptying gallbladder, the present analysis was undertaken. This paper is confined to observations on the significance of the delayed emptying gallbladder, the pathologic vesicle not being considered. No attempt is made to point to any one etiologic factor, as the problem is too complex. The purpose is to present, (1) statistics defining the measurements of the degree of contraction of the normal and delayed emptying gallbladder, (2) the complex etiology, (3) relationship of emptying of the gallbladder with emptying of the stomach, (4) relation of gastrointestinal disturbances, (5) effect of antispasmodics, (6) relation of position and tone of the gallbladder, (7) effect of thyroid, allergy and other conditions on the function of the gallbladder, and (8) its clinical significance as a provocative factor responsible for symptoms.

A large number of clinical cases with apparent gallbladder symptoms reveal functional changes without any other signs of pathology. One must be cautious in recommending surgical exploration in all cases of delayed emptying gallbladder, because of the frequent post-operative failure to relieve the symptoms. Eight of our cases were operated on, and in 7 the gallbladder was normal, in one case there was a band of adhesions between the gallbladder and pylorus. In the latter case, the operation did not relieve the symptoms. Car-

ter, Greene and Twiss state that about 70 per cent of patients with gallbladder symptoms do not have gall stones, but show evidence of disturbance in the emptying mechanism without the loss of concentrating function. Hellstrom found 30 per cent and Doubilet 40 per cent had post-operative symptoms similar to those prior to operation. The post-cholecystectomy syndrome occurred most frequently in those cases which presented functional disturbances demonstrated by cholecystography. Cole and Rossiter reported a few operative cases on poor emptying but otherwise normal gallbladders which revealed evidence of adhesions or some abnormality of the cystic duct.

The emptying of the gallbladder is a co-ordinated mechanism of the biliary tract. The emptying begins from 3 to 5 minutes after a fat stimulus with contraction of the gallbladder. There is a relaxation of the neck, cystic, and common ducts with opening of the sphincter of Oddi. The sphincter of Oddi regulates the passage of bile through the biliary tract into the duodenum. Spasm of the sphincter of Oddi produces delayed emptying, which may produce a hypertonic compensatory stasis. The administration of trinitroglycerin or the inhalation of amyl nitrite may relax the spastic sphincter of Oddi and accelerate the flow of bile from the gallbladder. Amyl nitrite and octyl nitrite inhalations given in 12 of our cases, proved to be ineffective. Atropine sulfate 1/100 grain or/and Syntropan 25 mg. given orally in 20 cases had no effect on the emptying of the sluggish gallbladder. Ivy also noted that a distended gallbladder frequently does not evacuate after spontaneous or artificial opening of the sphincter of Oddi.

The following etiologic factors are thought to be responsible for sluggish emptying of the non-calculus gallbladder; (1) abnormal elaboration of the hormone (cholecystokinin), (2) excessive thick mucus, (3) muscular changes in gallbladder wall, (4) spasm of the cystic duct, (5) kink of neck of gallbladder, (6) abnormal reciprocal mechanism of the gallbladder, duodenum and sphincter of Oddi, (7) unusually thick bile, (8) reflex, (9) nerve dysfunction, (10) adhesions, (11) digestive disturbances, (12) pylorospasm, (13) pyloric obstruction, (14) duodenal stasis or ileus, (15) endocrine i.e. hypothyroid, (16) allergy, (17) pregnancy, (18) drugs, i.e. morphine.

The condition is slightly more prevalent in women. In 75 cases 45 were female and 30 males. Westphal is of the opinion that women are more prone to nervous dysfunction and therefore are subject to hypophyseal or gonadal hormonal disturbances. He noted that in pregnancy there is a distended hypertrophic gallbladder with sluggish emptying. Casellas emphasized that biliary stasis is most pronounced in the viscerotonic

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individual, but this is not in accord with our experiences. We have noted that delayed emptying due to excessive accumulation of mucus admixed with tenacious gallbladder bile is a frequent cause of biliary dysfunction. Stasis may occur in hypercholesteremia as a result of the formation of inspissated bile. Changes in the acidity of the stomach, hypochlorhydria and achylia may in some instances produce delayed emptying. In a previous study of 110 cases of peptic ulceration with high gastric acidities, 35 revealed a sluggish emptying gallbladder. Metabolic changes are often causative factors in poor contractility of the gallbladder. Delayed emptying may be encountered in cases of obesity, and is a frequent finding in hypothyroid cases. In 8 cases, a Basal Metabolism test was made. 6 revealed a minus 20 to 30, and in 2 the rate was normal. Simendinger has experimentally shown that a distended gallbladder with thick viscid bile and delayed emptying was observed in thyroidectomized animals.

Functional disorders are due to intrinsic or extrinsic causes. If intrinsic, there may be diminished muscular contraction causing sluggish emptying, dilatation and a hypotonic gallbladder. The hypotonic gallbladder is large, pear-shaped or rounded. This type concentrates the dye normally and because of its lessened tone, empties sluggishly. The average size of the hypotonic vesicle is 4.8 by 6.5 centimeters; following a fat meal, 4.4 by 6 centimeters.

The atonic gallbladder is large, thin-walled, usually high in position, hugs the liver closely. It concentrates the dye normally, but due to the muscular atony, the expulsive mechanism of the gallbladder is weakened. The diameter varies between 5 and 8 centimeters with a more or less circular configuration. In the hypotonic and atonic types the loss of muscular tone, results in a large relaxed flabby vesicle.

In the hypertonic gallbladder the dysfunction is generally due to changes in the sphincter of Oddi. There

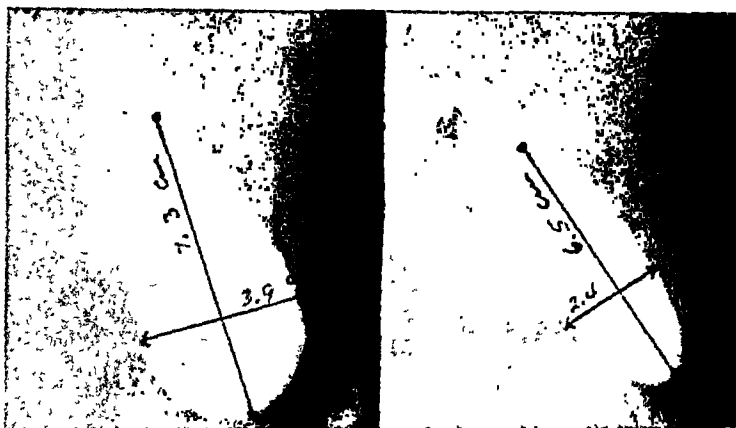


Fig. 1. Normal gallbladder; demonstrates normal dimensions; note the degree of contraction 30 minutes after a fat meal.

Allergy is a variable factor in functional disturbances of the gallbladder. In two cases an allergy to eggs was the primary cause of delayed emptying. These patient's symptoms became markedly exaggerated immediately following the egg meal.

The normal gallbladder is pear-shaped, concentrates the dye within 12 to 20 hours, and is visible as a dense homogeneous cholecystogram. In a study of 50 normal gallbladders, 44 were of normal tone, and 6 were hypertonic. Of these 42 were pear-shaped and 8 tubular. The normal gallbladder usually contracts to less than half of its original size within 30 minutes after a fat meal. This meal, two eggs and a glass of milk, is a physiologic stimulus, acting indirectly by elaborating cholecystokinin, a specific hormone for the emptying of the gallbladder. Evacuation is produced by a simultaneous muscular contraction of the gallbladder and relaxation of the sphincter of Oddi. The normal gallbladder usually contracts in all dimensions. The average size of the 50 normal functioning gallbladders is 3.8 by 7.9 centimeters; following the fat meal the vesicle contracts to 2.4 by 6.8 centimeters. The mean contraction was 1.4 centimeters in the transverse diameter and 1.1 centimeters in length.

is an interference to the flow of bile at the outlet, producing a compensatory enlargement of the gallbladder. This condition may cause a dilatation of the entire biliary tract. The hypertonic gallbladder is large, tubular, or elongated. Its walls are thickened and hypertrophied. There is an increase in tone, with normal concentrating function. The average size is 4.6 by 9.3 centimeters; after a fat meal, 4 to 8.7 centimeters.

In 75 cases of sluggish emptying gallbladders, 27 were of normal tone, 28 hypertonic and 20 hypotonic. Carter et al., found a hypertonic gallbladder in 25 per cent and hypotonic in 15 per cent of cases.

In our 75 cases the measurements of the sluggish emptying gallbladder yielded the following results. The average measurement of the filled vesicle is 4.4 centimeters in diameter by 8 centimeters in length. Following a fatty meal, the average size is 3.9 by 7.5 centimeters, giving a mean contraction of .05 centimeters in both dimensions. Comparing the average contraction of the normal series with the sluggish emptying gallbladder, one finds that in the normal gallbladder the contraction is almost three times greater in the transverse dimension and slightly over twice in length.

The shapes of the sluggish vesicles were rounded in 13, tubular in 21, and pear-shaped in 41 cases. The position of the gallbladder varied; 59 were between the twelfth dorsal and third lumbar vertebra; 15 on the level of the fourth lumbar and one on the level of the fifth lumbar. In the 75 sluggishly emptying gallbladders the density was exceptionally good in all instances. This indicates that the integrity of the mucosa and the ability of the gallbladder to concentrate the dye was unimpaired.

Forty-five of the 75 cases were studied for five, eighteen and twenty-four hours after a fat meal. No dye was visible in 5 cases. In 8 the dye was visible in the gallbladder in five hours, 20 in eighteen hours and 12 in twenty-four hours.

Of the 50 normal gallbladders, 32 were studied to determine the time of emptying. In 20 no dye was visible in five hours, 8 revealed dye in the gallbladder in five hours, 1 in eighteen hours and 3 in twenty-four

digestive disturbances. It is interesting to note that in 31 cases there were attacks of an acute nature in which 29 revealed abdominal pain radiating to the back; in 36 cases it was not localized. In 1 case there was a mild jaundice.

Gastrointestinal studies were made in 56 of the 75 cases; 26 were negative. Fifteen revealed definite gastrointestinal pathology, 13 showed functional changes. The genito-urinary tract accounted for the symptoms in 5 cases. It is noteworthy that 31 patients in this series of 75 cases had previous surgical explorations, 19 of these being appendectomies without the relief of symptoms.

CONCLUSION

The sluggish emptying gallbladder presents a clinical problem of the greatest diagnostic and therapeutic import. The significance of the sluggish emptying gallbladder as judged by cholecystography must be inter-

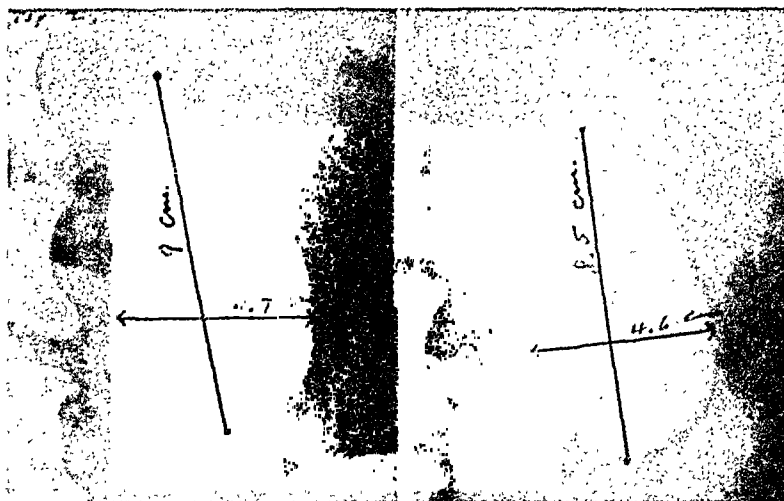


Fig. 2. Sluggish emptying gallbladder; large pear-shaped, well-filled gallbladder. Note the lack of contraction after a fat meal.

hours. It is noteworthy to point out the marked difference in the time visibility of the normal and the delayed emptying gallbladder. Of the 45 sluggish emptying gallbladders, 40 showed a visible shadow over a long period, while in 32 normal gallbladders only 12 cases showed persisting visibility. It is evident that the emptying mechanism is significantly impaired in the sluggish emptying group. The persistent visible vesicle is not only due to the delay in emptying but the factor of re-absorption of dye must be considered.

In 25 of the 75 sluggish emptying gallbladders a gastrointestinal study was made to determine the time of emptying of the stomach in relation to the emptying of the vesicle. Twenty of the stomachs emptied normally and 5 revealed a small gastric residue in five hours. Retarded emptying of the stomach may possibly play some role in the delayed emptying gallbladder, but in this series of cases the retention was too small to interfere with the normal function of the gallbladder.

Some of the cases gave a more or less typical history of gallbladder disease. However, all presented

interpreted as a functional phenomenon. It is important to emphasize that this functional change may be a causative factor in the production of digestive symptoms, because of lack of bile necessary for normal digestion.

The complex etiologic factors causing delay in emptying of the gallbladder offers a perplexing problem. Attention must be directed to the many extrinsic factors which may be responsible for this condition. These cases should be treated individually on the basis of a complete study. Surgical exploration should be attempted only as a last resort, since many of these cases are not relieved by operation.

In a study of 396 consecutive cholecystographic examinations 75 or 19 per cent revealed a poorly contracting gallbladder without other vesicle abnormality. An attempt is made to establish a normal measurement of the gallbladder with a comparative study of the sluggish vesicle. The relation of disturbance of the digestive tract with the delayed emptying gallbladder is discussed. Statistics on the persistence of the gallbladder shadow in both the normal and sluggish emptying is given.

A study of the 75 cases of sluggish emptying gallbladders showed the following pertinent facts; (1) unusually high incidence, (2) extrinsic factors often responsible, (3) transient nature of the functional changes, (4) normal vesicle wall with normal concentration of dye, (5) visibility of the gallbladder over long periods of time, (6) no pathologic change other than poor emptying, (7) it may or it may not be responsible for digestive disturbances.

TABLE
PREDOMINANT CLINICAL FINDINGS

Acute attacks	31
Epigastric pain radiating to back and shoulder blades	29
Abdominal pain or distress (not localized)	36
Chills and fever	3
Appetite . . . good 55, poor	9
Food relief	15
Bowels . . . diarrhea 10, constipated	25
Nausea . . .	11

Vomiting	23
Gas and abdominal distention	20
Burning	4
Jaundice	1
Liver, slightly enlarged	3
Allergy	2
Thyroid disease	4
Gastrointestinal examinations	56
Negative	26
Duodenal ulcer	12
Spastic, irritable G. I. tract	13
Gastric ulcer	1
Right upper quadrant adhesions	2
Carcinoma of stomach	2
Genito-urinary	5
Kidney stones	4
Ureteral stones	1
Operations	30
Appendectomy	19
Gynecological	9
Thyroid	1
Kidney removed	1

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An Attempt to Prevent Histamine-Induced Ulcers in Guinea Pigs with Benadryl (Beta Dimethylaminoethylbenzhydryl Ether Hydrochloride)*

By

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IT HAS BEEN shown that gastric and duodenal ulcers can be produced in a variety of laboratory animals by the intramuscular injection of a histamine-beeswax mixture (1, 2). Six of 8 guinea pigs so treated by Hay and others died of perforated gastric or duodenal ulcers (2). These workers were of the opinion that the predominating action of histamine was the stimulation of the acid-producing gastric cells, and that the unopposed action of the hydrochloric acid resulted in digestion of the gastric and duodenal wall.

Loew and others (3, 4), in 1945, showed that the compound benadryl exhibited the property of preventing or at least alleviating some of the pharmacologic actions of histamine, particularly antagonizing the spasmodic effects of histamine on the smooth muscle of the bronchioles of guinea pigs.

The purpose of the experiment here described was to determine if benadryl would prevent the formation of gastric and duodenal ulceration induced by prolonged administration of histamine.

METHODS

1. *Animals*: Sixteen adult albino guinea pigs of both sexes weighing between 300 and 650 grams were used in this study.

2. *Histamine in beeswax suspension*: Dessicated histamine dihydrochloride was suspended in mineral oil and beeswax according to the procedure outlined by Hay and co-workers (2).

3. *Control Animals*: In each of 8 guinea pigs, 0.05 cc. histamine suspension (containing 100 mg. of histamine base per cc.) was injected into the lumbar muscles daily for eleven days. For the next six days, 0.1 cc. of the histamine suspension was administered daily to the surviving animals.

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Treated Animals: Each of 8 guinea pigs was given the same dosage of histamine suspension as was given to the control animals. The treated animals were also given a total of 135 mg. per Kg. of body weight daily of benadryl, intraperitoneally, administered in sterile water. This solution contained .005 Gm. per cc. This was administered in divided dosages of 25 mg. per Kg. every four hours, 5 times a day, with an additional 10 mg. per Kg. preceding the increased interval of eight hours each night. It has been shown

no correlation between perforation and size of the ulcer. In one instance, there was minimal mucosal hemorrhage surrounding the ulcers. There was no significant difference in the total number of ulcers in the two groups. Occasionally there was considerable edema and acute inflammatory cellular infiltration in the submucosa beneath and near the ulcers. There was no microscopic evidence that vascular occlusion had contributed to the production of the ulcers. Other than the peptic ulceration, and the secondary peritonitis

TABLE I. Peptic Ulceration in Histamine-Treated Guinea Pigs

Survival in days	Ulcer	Remarks
Control Group		
3	Yes	Expired. Peritonitis. 2 perforated ulcers, 1 in duodenum and 1 on greater curvature.
3	Yes	Expired. Peritonitis. 1 perforated and several nonperforated ulcers on greater curvature and duodenum.
3	Yes	Expired. Peritonitis. Perforated ulcer on greater curvature.
3	Yes	Expired. Peritonitis. 3 perforated duodenal ulcers.
17*	Yes	Sacrificed. 2 ulcers on greater curvature.
17*	Yes	Sacrificed. 2 ulcers on lesser curvature.
17*	No	Sacrificed. No ulcers.
17*	No	Sacrificed. No ulcers.
Benadryl Group		
1	Yes	Expired. Peritonitis. 6 ulcers on greater curvature, 2 perforated.
2	Yes	Expired. Peritonitis. 3 ulcers on greater curvature, 2 perforated, 1 duodenal ulcer.
7	Yes	Expired. Peritonitis. Perforated duodenal ulcer. 6 ulcers in stomach and duodenum.
8	Yes	Expired. Peritonitis. Perforated ulcer on greater curvature.
17*	Yes	Sacrificed. 1 ulcer on greater curvature.
17*	No	Sacrificed. No ulcers.
17*	No	Sacrificed. No ulcers.
17*	No	Sacrificed. No ulcers.

*Sacrificed.

that benadryl in doses of 25 mg. per Kg. is sufficient to protect guinea pigs against anaphylactic shock (5).

Daily injections of both benadryl and histamine was continued for seventeen days, at the end of which time the surviving animals were sacrificed and complete autopsies performed. The animals receiving benadryl were depressed and lethargic, but moved when stimulated.

RESULTS

The results of this experiment appear in Table I. Five of the 8 (62%) benadryl-treated animals showed ulcers, and in 4 animals perforation had occurred. Six of the 8 (75%) control animals showed ulcers, and in 4 these had perforated. All ulcers were of the acute type, were frequently multiple, and tended to be most numerous in the cardiac end of the stomach and on the greater curvature. The size of the ulcers varied from 0.25 mm. to 4.0 mm. in diameter, and there was

in many animals, no significant histologic lesions in either group of animals were encountered.

COMMENT

It has been suggested that benadryl be used in the management of peptic ulcer (6) since it has been shown that this substance has a depressant effect upon the gastric acidity in human subjects (6, 7). However, 50 mg. per Kg. of benadryl administered subcutaneously to dogs did not significantly reduce the response of the gastric glands to injection of histamine (8). The dosage of benadryl used in this experiment, although effective in preventing anaphylaxis in sensitized guinea pigs (5), did not appear to influence the production of gastric and duodenal ulcers in histamine-treated guinea pigs.

SUMMARY

Treatment with benadryl does not prevent histamine-induced ulcers in guinea pigs.

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Some Effects of High Lipid Diets on Intestinal Elimination

IV. Saturated Fatty Acids

By

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IN A PREVIOUS investigation made in this laboratory (1) some effects on intestinal elimination were noted when diets rich in glycerides of saturated fatty acids were fed to dogs. These effects included the following: (1) constipation, when diets containing large amounts of simple triglycerides of high molecular weight (tristearin and tripalmitin) were fed; (2) diarrhea, when small amounts of simple triglycerides of acids having twelve or less carbon atoms were fed. However, the addition to the diet of as much as 20 per cent trimyristin had no effect on intestinal elimination at all. Chemical analyses showed greater than normal amounts of lipids present in the feces when the glycerides fed melted above body temperature (tristearin, tripalmitin, trimyristin, trilaurin).

Several years ago, Bosworth, Bowditch and Giblin (2) noted that bottle-fed infants receiving diets too high in fat content were subject to vomiting and diarrhea. These investigators found increased quantities of calcium soaps present in the feces of such infants and attributed the gastro-intestinal behavior of the infants to the presence of these soaps. They also claimed that the fecal lipids would be further increased in such cases by neutral fats being occluded in the soaps.

Duell, Hallman and Reifman (3), who determined the rate of absorption of fatty acids in the rat found that butyric, caproic and caprylic acids fed as sodium salts were rapidly absorbed from the intestine, while capric acid (uncombined) was absorbed more slowly. Lauric acid became solidified and remained in the stomach so that it was absorbed very slowly. Lyman (4), feeding basic diets fortified with lard, ethyl palmitate, glyceryl tripalmitate, or palmitic acid to two dogs reported that the per cent of fatty acid (actually the ether extract) in the feces after ethyl palmitate or palmitic acid was much greater than after tripalmitin or lard feedings. He attributed the increase in ether extract to undigested ethyl palmitate in the first case, but the increase in palmitic acid when that lipid was fed could not be attributed to undigested material since no digestion was required. He, therefore, assumed that free fatty acids disturb the mechanism of digestion because they are irritating to the digestive tract, causing the food mass to be discharged more slowly from the stomach, but probably increasing peristalsis and the amount of feces.

Telfur (5), studying one normal infant and three

with biliary atresia and obstructive jaundice, found that when bile is completely excluded from the gut, over 70 per cent of the dried feces are composed of fatty derivatives. Further, the non-absorption and persistence of excess fatty acids in the intestine are associated with modifications of the normal calcium and phosphorus excretion. Calcium is present in the feces in excess of normal, while phosphorus, released from calcium, is absorbed and eliminated in the urine. The extent of the variation is said to depend on the concentration of free fatty acids in the intestine.

While the preceding investigators believed that a relationship existed between dietary fat, fecal lipids and, in some cases, intestinal behavior, other investigators found no relation between ingested fats and fecal fat. Krakower (6), using eight fracture patients with good elimination habits as subjects, fed normal, low fat and special diets containing added corn oil (Mazola) or added coconut oil (Nucoa) for 4-day periods. Finding no correlation between the dietary fat and the total fat content of the feces or its composition as determined by the iodine number, he concluded that fecal lipids do not represent the residual food fat when moderate or larger amounts of fat are fed. Hill and Bloor (7), basing their conclusions on observations of four cats, decided that when moderate amounts of fat are fed, the fecal fat is independent of the diet, and that fecal fat ordinarily cannot be regarded as unabsorbed fat. They found the fecal lipids to consist principally of fatty acids and their salts (soaps) with smaller amounts of cholesterol and its derivatives and a little fat. They attributed the larger amounts of fat and fatty acids present in the feces after a high fat diet to unabsorbed food fat. Holmes and Kerr (8), using human subjects, also found the fecal fat to be different from that of the diet.

Because some of these investigators had attributed variations in either the behavior of the intestines or in the lipid content of the feces to the presence of unabsorbed fatty acids or calcium salts of fatty acids, it was decided to feed some of the fatty acids, the glycerides of which had been used in our previous experiment.

PROCEDURE

Four healthy male dogs*, the subjects in the previous experiment, were fed experimental diets. During this experiment, these dogs were kept indoors in sep-

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*Dog X, a thirty-pound, part-spaniel; Dog C, a mixture of beagle and collie, weighing about twenty-three pounds; and two fox terriers R and W, weighing seventeen and thirteen pounds, respectively.

arate cages, from which they were removed for periods of exercise. All were fed once a day and at the same time. Originally all of the dogs were given a diet of canned Pard* Dog Food, but when this article disappeared from the local markets, Dog X was fed dried food in order to conserve the scarce tinned Pard for the dogs used for the quantitative determinations. The smaller dogs, C, W, and R, were each fed the contents of a one-pound can of Pard each day. When fatty acids were to be introduced into the diet, the contents of a can of Pard (454 gm.) were thoroughly mixed with the calculated amount of acid in a mortar. The dog was then allowed to eat directly from the mortar in order to avoid loss of material through a transfer to another dish.

The large dog X, as in the previous investigation, was used principally to test the palatability of the special diets. When this dog refused to eat the food or became ill after eating it, the concentration of added fatty acid was diminished to a point where such effects were not observed before the diet was fed to the remainder of the dogs. If the dogs did not eat all of the special diets, the food was removed from the cage after half an hour. The dogs were not fed again till the next regular feeding time, 24 hours later.

When the special diets were fed, information about the intestinal behavior of the animal was obtained, as in the previous investigation, by direct observation of the animal and by chemical examination of the feces. The fecal material was collected for examination and analysed as quickly as possible after defecation in order to avoid changes in water content.

The special diets were fed for three consecutive days; the second day's ration being identified by a marker, so that the time required for the food to pass through the intestines could be easily noted.

Chemical analyses, run on the sample after mixing and grinding in a mortar until homogeneous, included moisture, total lipids, lipids soluble in neutral ether and soap fat. Iodine and acid numbers were determined on the three lipid fractions.

Moisture determinations were run simultaneously with lipid determinations in a Kaye extraction apparatus with mercury seals (9). Lipids soluble in neutral ether were extracted for twelve hours with neutral isopropyl ether, soap fats were then removed by extracting the residues for twelve hours with decinormal acid isopropyl ether. Total lipids were obtained by extracting the original samples with decinormal acid isopropyl ether for twenty-four hours and the values compared with the sum of the lipids soluble in neutral ether and soap fat for the same fractions.

All of the lipid fractions were purified by shaking at frequent intervals with petroleum ether, during a period of eight hours. The fractions were then filtered, the solvent distilled off and the residue dried in a vacuum dessicator over concentrated sulfuric acid. Iodine numbers (Wij's Method) and acid numbers were determined for the purified lipid fractions.

*Sufficient canned Pard Dog Food to complete these studies was furnished us by the Research Division of Swift and Company.

DISCUSSION AND RESULTS

Because the dogs had eaten a diet of Pard containing 20 per cent added tristearin in the previous investigation, an attempt was made to feed a diet of Pard to which 20 per cent stearic acid had been added. However, the dogs refused to eat such a diet and not until the stearic content had been reduced to five per cent would they eat their food at all. On the second day, all of the dogs were badly constipated, listless and had elevated temperatures. They refused to eat all of their rations, the amount left being inversely proportional to the size of the dog (W, 200 g.; R, 100 g.; C, 78 g.). On the third day, the symptoms of the previous day were still present, and the dogs refused to eat at all. Twenty-four hours later, the animals seemed to have recovered and ate their normal Pard diet.

Table I contains the analytical data for the fecal material in which the marker for the second day of the stearic acid diet appeared. For the purpose of comparison, data for the tristearin diet, as well as the normal diet, have been included.

Inspection of Table I shows that the addition of as little as five per cent stearic acid to the usual Pard diet of the dogs caused a reduction in the moisture content of the feces. The total lipid content of the feces of two of the dogs was less than when Pard diet alone was fed. The per cent of neutral ether extract increased in every case, and the per cent of soap fats diminished, just as was the case when the triglyceride of stearic acid was added to the diet. However, the total amount of soap present after the feeding of a diet containing 5 per cent added stearic acid was greater than after the diet with 20 per cent added tristearin.

The analytical constants of the fractions furnish little information about the composition of the lipids in the fractions. However, it can be said that the soaps isolated from the feces after feeding stearic acid do not consist primarily of stearic acid salts, since the acid numbers indicate material of much higher molecular weight.

The acid numbers ranging from 43.7 to 50.4 indicate molecular weights from 1283 to 1113, respectively, while the molecular weight of stearic acid is only 284. It, therefore, seems probable that, when stearic acid is fed, a great deal of the so-called soap extract in the feces does not consist of soaps of fatty acids at all.

The iodine numbers indicate a greater degree of unsaturation in the soap fraction when stearic acid was fed, than when either the Pard alone, or Pard with tristearin was fed.

Since there was no increase in calcium soaps in the feces even when stearic acid itself was added to the Pard diet, it seems reasonable to conclude that constipation resulting from a diet rich in tristearin or stearic acid is not caused by the presence of unabsorbed calcium soaps.

TABLE I
Analytical Data From Feces of Three Dogs Fed Tristearin and
Stearic Acid in Measured Quantities

Diet	Dog	Per Cent Moisture	Per Cent Lipids			Iodine Numbers			Acid Numbers			
			Total Lipids	Neutral Ether Extract	Soap Fat by Extraction	Soap Fat by Diff.	Total Lipids	Neutral Ether Extract	Soap Fat	Total Lipids	Neutral Ether Extract	Soap Fat
Pard	C	69.9	20.3	2.9	18.0	17.4	8.0	27.2	5.6	52.8	49.4	59.9
5% Stearic Acid		64.3	9.3	6.2	3.3	3.1	26.4	23.2	31.2	20.1	12.5	43.7
20% Tristearin		40.8	50.5	46.8	1.4	3.7	5.2	1.9	17.3	16.0	185.1	54.2
Pard	R	73.9	19.3	9.3	7.6	10.2	5.1	6.4	25.1	48.6	38.9	54.2
5% Stearic Acid		68.2	15.3	10.4	5.0	5.1	20.3	18.4	42.6	23.6	15.4	48.0
20% Tristearin		36.2	27.4	21.6	1.6	5.8	7.7	3.5	19.0	40.6	37.8	74.3
Pard	W	74.8	17.4	5.0	13.1	12.4	12.9	18.2	12.0	36.2	29.1	43.4
5% Stearic Acid		69.8	27.6	16.4	10.5	11.2	16.4	12.8	53.4	18.3	14.7	50.4
20% Tristearin		54.7	47.6	39.4	0.9	8.2	5.6	5.5	35.6	46.5	37.1	118.5

Because the dogs had all been made ill by the addition of five per cent stearic acid to the Pard diet, the experiment was not duplicated with palmitic acid. However, Dog C was fed a diet of Pard to which nine-three days all of the dogs ate a diet of Pard containing

ten per cent additional lauric acid. During this period, the dogs were in good health and intestinal elimination was regular. The feces appeared normal in shape and consistency. It will be recalled that a Pard diet with 20 per cent added trilaurin in the previous

TABLE II
Analytical Data From Feces of Dog C Fed Tripalmitin and
Palmitic Acid in Measured Quantities

Diet	Per Cent Lipids					Iodine Numbers			Acid Numbers		
	Per Cent Moisture	Total Lipids	Neutral	Soap Extract	Soap Fat Difference	Total Lipids	Neutral Ether	Soap Extract	Total Lipids	Neutral Extract	Soap Extract
			Extract								
Pard	69.9	20.3	2.9	18.0	17.4	8.0	27.2	5.6	52.8	49.4	59.9
Pard+0.9% Palmitic	70.6	18.4	12.0	4.7	6.4	36.2	16.7	-	155.7	194.2	154.3
Pard+20% Tripalmitin	63.5	56.9	42.7	9.8	14.2	5.3	7.4	8.4	96.6	83.8	201.2

tenths of a per cent palmitic acid was added. After this diet had been fed for three days, elimination was still normal. Analytical data for the feces included in Table II are not particularly informative.

The feeding of a meal of Pard to which lauric acid

had been added was not difficult to accomplish. For investigation (1) caused diarrhea with feces only semi-solid in consistency.

Table III contains the analytical data for the fecal material eliminated after the feedings of Pard with

TABLE III
Analytical Data From Feces of Dogs Fed Trilaurin and
Lauric Acid in Measured Quantities

Diet	Dog	Per Cent Lipids					Iodine Number			Acid Number		
		Per Cent Moisture	Total Lipids	Neutral Ether Extract	Soap Fat by Extraction	Soap Fat by Difference	Total Lipids	Neutral Ether Extract	Soap Fat	Total Lipids	Neutral Ether Extract	Soap Fat
Pard	C	69.8	20.3	2.9	18.0	17.4	8.0	27.2	5.6	52.8	49.4	59.9
10% Lauric		48.9	12.3	7.4	5.0	4.9	15.1	12.7	16.5	18.0	15.0	42.4
20% Trilaurin		31.2	* 54.6	42.0	12.6	---	---	14.4	26.8	---	125.8	187.5
Pard	R	73.9	19.5	9.3	7.6	10.2	5.1	6.4	25.1	48.6	38.9	54.2
10% Lauric		68.8	14.6	8.4	6.3	6.2	13.9	11.2	15.4	18.4	17.4	42.9
20% Trilaurin		78.4	13.0	9.3	1.5	3.7	23.0	22.8	48.1	241.2	199.7	214.8
Pard	W	74.8	17.4	5.0	13.1	12.4	12.9	18.2	12.0	36.2	29.1	43.4
10% Lauric		72.0	13.6	7.4	6.1	6.2	13.9	12.4	17.4	18.7	19.4	46.3
20% Trilaurin		79.7	18.8	15.1	2.0	3.7	17.6	18.3	36.0	235.7	200.8	244.3

*Total Fat by Calculation.

lauric acid. Data from the trilaurin diet are added for ease in making comparisons.

Inspection of Table III reveals a slight reduction in moisture content in the case of the two terriers and a marked reduction for Dog C. This is in decided contrast to the increase in moisture content after the feeding of the triglyceride of lauric acid.

The agreement between similar lipid fractions obtained from the feces of all three dogs on the lauric acid diets should be noted. In all cases, the percentage of total lipids is less than when Pard alone was fed. The extremely low acid numbers of all the soap fractions show that lauric acid (or its salts) is not the principal component of the fecal fat when the acid is fed. An acid number of 42.4 indicates a molecular weight of 1323; lauric acid has a molecular weight of 200. This, again, is a contrast to the soap fat of the feces after feeding the glyceride of lauric acid. The

containing two per cent butyric acid (about 1 gm. in a pound of Pard). Following this feeding, the stools were pasty. Only part of one feeding of a mixture of Pard with four per cent butyric acid was eaten by Dog X. This feeding gave rise to pasty stools with much fluid. No chemical analysis of the stools was attempted.

The analytical data for the feces collected after diets with added caprylic and caproic acids are included in Table IV. The lipid content was much the same after the feeding of caprylic acid or its triglyceride in the concentrations used. Caproic acid, fed in the same concentration as caprylic acid, resulted in much larger quantities of fecal lipids than caprylic acid; in two cases more than the normal amount. Since the total lipids and not the soaps increased after the caproic acid

TABLE IV
Analytical Data From Feces of Dogs Fed Tricaprylin, Tricaproin,
Caprylic Acid and Caproic Acid in Measured Quantities

Diet	Dog	Per Cent Moisture	Total Lipids	Per Cent Lipids			Acid Numbers		
				Neutral Ether Extract	Soap Extract	Soap Fat by Difference	Total Lipids	Neutral Ether Extract	Soap Extract
Pard	C	69.8	20.3	2.9	18.0	17.4	52.8	49.4	59.9
5% Caprylic Acid		70.2	4.1	2.3	1.8	1.8	16.0	14.0	42.3
4% Tricaprylin		77.8	4.2	1.7*	1.1	---	88.6	93.7	95.4
5% Caproic Acid		70.1	25.0	18.3	6.7	---	17.3	14.0	42.5
2% Tricaproin		78.3	6.8	6.2	1.9	2.6	74.6	60.6	77.4
1% Tricaproin		76.3	5.1	3.6	3.0	1.5	155.4	141.9	106.6
Pard	R	73.9	19.5	9.3	7.6	10.2	48.6	38.9	54.2
5% Caprylic Acid		71.5	7.0	4.5	2.2	2.5	17.4	12.2	47.0
4% Tricaprylin		75.3	6.7**	5.7	1.0	---	---	91.2	108.8
5% Caproic Acid		72.8	22.4	16.9	5.4	5.5	15.2	12.0	43.0
2% Tricaproin		82.7	4.2	3.1	1.2	1.1	98.7	92.6	116.7
Pard	W	74.8	17.4	5.0	13.1	12.4	36.2	29.1	43.4
5% Caprylic Acid		73.2	2.9	2.5	0.8	0.4	18.2	20.1	49.1
4% Tricaprylin		76.8	7.8	6.4	0.7	1.4	108.3	91.4	128.5
5% Caproic Acid		71.9	13.4	9.5	3.8	3.9	14.0	11.4	47.1
2% Tricaproin		80.3	5.5**	4.7	0.8	---	---	69.6	123.4

*Mechanical Loss

**Total Fat by Calculation

higher acid numbers (187.5-244.5) indicate lower molecular weights (299-229) not too different from that of lauric acid (200). This is the best agreement between the molecular weight of the fatty acid fed and the molecular weight of the fatty acid in the material recovered from the feces of any lipid diet that we fed, excepting that of tripalmitin.

The dogs were reluctant to eat Pard containing added caprylic acid but finally consumed all of a mixture with five per cent of the acid. This diet, fed for three consecutive days, proved mildly laxative and caused semi-fluid stools.

No particular difficulty was encountered with a Pard diet containing five per cent added caproic acid for all of the dogs ate the diet with apparent relish. Following this diet, the stools were profuse, soft and pasty.

Three of the dogs could not be persuaded to eat Pard to which butyric acid had been added. Dog X, when denied other food, finally ate a mixture of Pard

feedings, it was at first suspected that the material might consist of unabsorbed caproic acid. However, the low acid numbers of the fractions indicate that free caproic acid was not present in the feces to any extent.

The low acid numbers of the soap fat present in the feces after the diets with caproic or caprylic acids indicate once more that calcium soaps are not formed in appreciable amounts, after large amounts of free fatty acids are fed.

The acid numbers of all of the soaps obtained from the feces of the three dogs after feedings with acids are in remarkable agreement. The only exception is the case of palmitic acid where less than one per cent was fed. If this acid is omitted from the list, the highest acid number of the soap fats is 50.4, obtained when stearic acid was fed to the smallest dog; the lowest value is 42.3, obtained when caprylic acid was fed to the largest dog. The average value for all dogs and all acids is 45.4. These acid numbers correspond

to molecular weights of 1113, 1326 and 1235, respectively, a finding which strongly indicates that the materials did not contain any appreciable amount of fatty acid soaps. Samples of the so-called soap fats have, therefore, been preserved for further chemical analyses.

SUMMARY

1. Measured amounts of fatty acids mixed with a standard dog food (Pard) were fed to dogs to determine whether intestinal elimination would be affected by the added acid in the same manner as by the addition of the corresponding triglyceride.

2. Stearic, lauric, caprylic, and caproic acids were the acids mixed with the standard dog food and fed to all the dogs. One dog received feedings containing less than one per cent added palmitic acid; another ate a single feeding of Pard with added butyric acid.

3. Information concerning the intestinal behavior of the animals was obtained in two ways: (1) direct observation of the animal; and (2) chemical examination of the feces.

4. Chemical components of the feces for which analyses were made included moisture, total lipids, neutral ether extract and soap fat. Acid numbers were determined for all lipid fractions after all feedings; iodine numbers were determined after stearic and lauric acid feedings.

5. Constipation was produced by 5 per cent added stearic acid.

6. The neutral ether extract increased for every animal after the 5 per cent stearic acid feedings but the so-called soap fat was less than the normal value in every case.

7. The addition of 10 per cent lauric acid to the normal diet did not affect the normal rate of elimination of the dogs.

8. The feeding of diets containing caprylic, caproic or butyric acid produced laxative effects in all cases.

The intensity of the action varied inversely with the number of carbon atoms just as in the case of the triglycerides of the corresponding acids. The moisture content of the feces did not vary greatly from the normal values when caprylic or caproic acid was added to the diet. No quantitative estimations were made after feeding butyric acid.

9. The acid numbers of all of the fatty acids from the soap extracts, with the exception of the one palmitic acid experiment, ranged from 42.3 to 50.4, with an average value of 45.4. These values correspond to molecular weights of 1326, 1113 and 1236, respectively.

CONCLUSIONS

The effect of a high fat diet on intestinal elimination depends at least partially on the component acids of the fats fed. Dogs fed pure saturated fatty acids behaved in approximately the same manner as when fed the corresponding pure triglycerides. Diarrhea resulted from the feeding of diets containing caprylic, caproic or butyric acids, or the glycerides of these acids. Constipation followed feedings of stearic acid or tristearin. Although trilaurin produced diarrhea, elimination was normal after feeding lauric acid.

These effects cannot be attributed to the presence in the feces of large amounts of free fatty acids or of soaps of the fatty acids, because the low acid numbers of the total lipid and neutral ether extracts exclude the possibility of large amounts of free acid. The low acid numbers of the soap fractions rule out the possibility of large amounts of soaps of fatty acids.

The low acid numbers of all of the fractions indicate that neither the fatty acid as fed nor its soaps are present in the feces to any extent. These low acid numbers can only be explained by assuming that small amounts of free fatty acids are mixed with large amounts of non-titratable material or by a very large molecule having an acid radicle.

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The Formation of Concretions of ³Aluminum Salts of Fatty Acids After the Use of Aluminum Hydroxide

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SINCE a careful search through the literature concerning the use of aluminum hydroxide for peptic ulcer failed to disclose any description of the formation of aluminum soap concretions, it was thought that the following observations would be of interest.

Aluminum hydroxide was used first by Crohn in this country in the treatment of peptic ulcer. He found no deleterious side effects. After the ingestion of 168 cc. of a heavy aluminum hydroxide suspension, Myers found less than 0.12 mgm.% in the blood stream. Quigley, Einsel and Meschan noted that large amounts of this substance when fed to animals over long periods had little if any undesirable side action.

Monaghan, however, reported that in persistent pylorospasm, large doses of aluminum hydroxide delayed the stomach emptying in many patients. Havens described one case of complete intestinal obstruction following the use of the antacid in the treatment of severe ulcer hemorrhage. He found at autopsy that a large mass of blood clot and aluminum hydroxide had completely obstructed the bowel.

Fauley and others have pointed out that aluminum chloride may be formed in the stomach and unless enough alkali is present in the intestine to convert the salt to the hydroxide, gastric and intestinal irritation may result. These apparent objections are few and aluminum hydroxide has enjoyed wide clinical use with remarkably satisfactory results. Bockus recommends, however, that in gastric stasis the rate of evacuation of this antacid from the stomach should be checked frequently.

The patient in whom the unusual aluminum concretions were found was a 36 year old male with a 15 year history of chronic duodenal ulcer. Following a severe hemorrhage in March 1945 the patient made an uneventful recovery on a bland diet with atropine and aluminum hydroxide medication. Three months after this hemorrhage and while still taking the antacid and maximum doses of tincture of belladonna he suffered another acute episode of severe pain culminating in hemorrhage. His stools were found to contain small formed white masses. These masses became more apparent after the melena had cleared up. Their passages were accompanied by intermittent periods of constipation

and diarrhea, cramps and pain suggesting intestinal irritation. The patient recalled a similar sequence of events with approximately the same interval between hemorrhages in 1941. At that time the white concretions were not analyzed.

This condition cleared up after five days. During this time, however, he passed about 40 small masses which were egg shaped and varied from 5 to 25 mm. in length. Their surface was convoluted bearing a hollow viscus impression. The color was white with yellow greenish lines in the crevices of the convolutions. On cutting, the cut surface was a pure white. Gross and microscopic examination showed no evidence of any organized structure. Their consistency was firm but somewhat rubbery. On drying the concretions they would shrink to two-thirds their former size but without any appreciable change in appearance.

The concretions burned readily with a yellow smoky flame leaving a considerable amount of ash.

They were only sparingly soluble in boiling chloroform, 10% aqueous sodium hydroxide or 10% hydrochloric acid. The chloroform extract gave a faint Liebermann Burchard test for cholesterol and the NaOH extract gave a very faint biuret test. An acrolein test was positive for glycerol. A small amount of material could be dissolved from the concretion with boiling alcohol. On evaporation of the alcohol, a greasy residue remained. This fatty residue gave negative tests for amines and phosphates.

On saponification with alcoholic KOH small whitish flakes of undissolved material remained. The flakes, as well as the ash which remained after burning a concretion, gave the usual qualitative tests for aluminum. On dilution with water and acidification of the alcoholic KOH solution remaining from the saponification, oily droplets of fatty acids separated from the solution.

These qualitative tests indicate that the concretions consisted of aluminum salts of fatty acids together with a small amount of neutral fat. There apparently was some water emulsified within the concretion judging from the diminution in size upon drying.

The site of origin of the aluminum soaps is open to speculation. Their size and surface markings indicate that the concretions were compressed in some hollow viscus of small bore. Their uniform texture and lack of admixture with other substances may be attributed to the relative absence of other substances in the gastro-intestinal tract of the pa-

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tient during the first days following the hemorrhage

The condition apparently cleared spontaneously when the patient was given increasing amounts of food.

SUMMARY

Following a hemorrhage of duodenal ulcer origin in a patient using aluminum hydroxide as an ant-

acid, small concretions were found in the stool. The passage of these concretions through the intestinal tract was accompanied by severe intermittent cramps and pain.

Chemical analysis of these concretions showed them to be composed of fatty acid salts of aluminum with a small amount of neutral fat and traces of cholesterol and protein.

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Management of Constipation with a Refined Psyllium Combined with Dextrose*

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FUNCTIONAL constipation constitutes one of the most challenging therapeutic problems in medical practice. "As everyone knows," asserts Alvarez (1), "the treatment is largely palliative and consists of making the stool more irritant, chemically or mechanically. All treatment must be palliative so long as the main cause of constipation, which is the strain and hurry of civilization, goes on unchecked." Bockus (2) declares that "obviously, the diet must be arranged to suit the individual requirements. If the colon is long and wide a greater amount of fiber may be needed to encourage normal elimination. On the other hand, in the short, comparatively narrow colon an excessive amount of fiber will often produce abdominal discomfort." Parsons (3) from a study of the effect of fiber in the human dietary concludes that elimination is entirely an individual problem (this is conceded by all), that it bears no relation to the amount of fiber present in the diet and that there may be a large daily variation in the amount of dry material evacuated. But Fantus, Kopstein and Schmidt (4) report that bran accelerated bowel

emptying in about 75 per cent of their patients.

Gary and Tainter (5) investigating hydrophilic colloids report that the tragacanth and the psyllium groups, consisting of the whole black psyllium seeds and various partly purified hemicelluloses, are most efficacious clinically and that they are most unlikely to produce side effects. Stein and Gelehrter (6), from a study of the effects of hydrogels on the configuration and function of the colon in twenty-two patients, conclude that both the atonic and spastic types of functional constipation are benefited. Mann (7), in a comparative study of liquid petrolatum and hemicelluloses, emphasizes the great superiority and advantages of the latter and further states that liquid petrolatum is unsatisfactory because it tends to (a) induce anal leakage, (b) lubricate the rectosigmoid thereby converting the proximal bowel into a reservoir for fecal material, (c) destroy the defecation reflex, (d) retard utilization of vitamin A (carotene) and perhaps other vitamins and (e) cause weight loss by interfering with assimilation.

These undesirable effects are not encountered when the hemicelluloses are employed. In a comprehensive study of karaya gum (Mucara-processed form) Ivy and Isaacs (8) determined that it increased the number of defecations as well as the urge to defecate and relieved 19 of 23 constipated persons. Brown and Dolkart (9) advocate the extensive use of processed *Plantago ovata* and dextrose for the treatment of bowel disturbances.

*Metamucil, supplied by G. D. Searle & Co.

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The valuable assistance of the following is gratefully acknowledged: Dr. Michael Indovian (Roentgenologist of the Chicago State Hospital and Alexian Brothers Hospital), and the following of the Chicago State Hospital; Drs. Benjamin Cohen and Herman Josephy (Staff Members) Carmelo Macaluso (Bacteriologist) and Jack Noonan (X-Ray Technician) the Superintendent and Nurses.

REFINED PSYLLIUM MUCILLOID AND DEXTROSE

Among the products of this type currently used in the treatment of constipation is one, Metamucil, which employs only the mucilaginous portion of the blonde psyllium seed. This psyllium mucilloid is that portion of the seed which comprises its coating or investment membrane; it is capable of absorbing a definite volume of aqueous liquids with the formation of a clear opalescent plastic gel. In the manufacturing process all irritating particles, such as wood fiber, seed husks and other extraneous material, have been removed. This preparation is a homogeneous mixture containing 50 per cent of the highly refined mucilloid of the psyllium seed (*Plantago ovata*-Forsk) and 50 per cent of powdered anhydrous dextrose (crystalline *d*-glucose. For purposes of palatability, traces of citric acid, sodium bicarbonate and monobasic potassium phosphate are added.

The value of such products in the treatment of functional constipation is conceded by most investigators. This consensus, however, is based on investigations of less refined preparations which have similar but not identical properties.

The present extensive investigation was undertaken to determine the effects of this mucilloid preparation (Metamucil) on the bowel and its contents, to evaluate its clinical effectiveness and to determine whether or not any side reactions occur during its continuous use in the management of constipation.

PROCEDURE

Forty subjects were selected for this study; 37 were inmates of the Chicago State Hospital (for mental and nervous diseases), 2 were employees and 1 a private patient. The inmates were picked from all the wards of the hospital so as to obtain as representative a group as possible.

A complete history was taken and a thorough physical examination was performed as well as complete blood counts, urinalyses, blood chemistry, stool studies and other indicated tests. The preliminary routine anorectocolon study consisted of inspection, digital and sigmoidoscopic examinations, and these were repeated at frequent intervals during a control and test period of observation. Simultaneously serial gastrointestinal roentgen studies were done, each ending with a double contrast barium enema.

During the first portion of the study all patients, except one, were hospitalized. None was hospitalized during the latter part of the observation, conducted six months later, when 16 patients of the original group were again observed, the emphasis being placed on determination of urine and blood changes and of blood sugar values, especially in those with diabetes.

The investigation was initiated with a control period of one week and was preceded by a thorough examination and, intensive inquiry, including hab-

its, physical findings, defects and results of various tests. Upon completion of the control period these procedures were repeated, and the patients were now given one rounded teaspoonful (4 Gm.) of Metamucil in water three times a day after meals for one week. Modifications of this routine were instituted as indicated by certain tests, clinical results and roentgenologic evidence.

The diet was nourishing and well balanced, the same as that served to all patients and hospital employees. The average daily intake of approximately 2,250 calories included 95.6 Gm. of proteins, 261.8 Gm. of carbohydrates and 71.1 Gm. of fats.

During the periods of investigation all foods and liquids were weighed, measured and recorded. The routine basic diet was consumed by all subjects except those with diabetes.

TYPES OF PATIENTS

The group of 40 subjects consisted of 22 men aged 33 to 77 years and 18 women aged 16 to 69 years; all had been institutionalized for periods of from eight months to thirty-eight years, with the exception of the 2 employees and the private patient. All patients were generally well nourished and developed. With the exception of those with diabetes none presented significant pathologic changes other than those characteristic of their respective neurologic disease. The latter included all the various types usually encountered in such institutions, with their well known tendency to chronic constipation.

Although in some instances the history of onset of symptoms was unsatisfactory, all were known costives for periods extending from early childhood to a few months; the last 3 complained of prolonged and intractable constipation. There were none who did not require some form of laxative or cathartic at frequent intervals.

Cooperation of 29 was excellent, of 7 satisfactory, but only 19 were able to fulfil the difficult requirement of collecting their feces. The 4 uncooperative ones were excluded from the second stage of the study so that the entire group performed satisfactorily.

One neurotic patient failed to collect stool specimens during the first period because evacuations were extremely infrequent, but specimens were available in the second period during which she was given increasing doses of Metamucil and thus a comparative study was obtained.

The condition of the teeth was good in 12 or 30 per cent; while in the remaining 70 per cent mouth hygiene was poor in 10 as a result of their being partly or completely edentulous and in 18 because of caries and badly fitting dentures.

Abdominal examinations revealed no rigidity or masses in any of the patients. Tenderness was evident in the right lower quadrant of 3, in the right upper quadrant of 8, left lower quadrant of 1 and generalized in 1. By repeated examinations the

abdomens were classified as flat in 15, pendulous in 14, moderately distended in 5 and slightly distended in 6.

RESULTS

During the control period only 11 (27.5 per cent) of the subjects had a daily evacuation considered relatively satisfactory, although in 2 of them the stool was hard and had to be forced out or the evacuation was incomplete. Among the remaining 29 (72.5 per cent) subjects 18 had bowel movements at intervals ranging from two to four days, 1 was uncertain, 1 was very irregular, 2 were untidy, 6 were unable to furnish reliable information and 1, an employee, had no evacuation for fifteen days.

During the treatment period, while taking Metamucil, 22 subjects (55 per cent) reported having a daily evacuation. Patients previously experiencing hard or incomplete evacuation were now entirely relieved. Three, of the remaining 18, had a bowel movement daily or every two days (including the completely obstipated employee). 1 every three or four days, 1 daily or twice daily, the 2 who had been untidy now had a daily evacuation and were entirely clean, 1 remained irregular, the same 6 patients were still unable to furnish reliable information but sigmoidoscopy revealed a completely or partially empty bowel and 4, who became extremely uncooperative in the second period of the study and failed to take the Metamucil regularly, had to be excluded.

Prior to treatment many patients had complained of discomfort, distress or actual pain during or after evacuation, described as "very marked", "sharp", "burning" or "cutting." These symptoms varied even in the same patient with respect to intensity, character and time. This group comprised 18 (45 per cent), 8 denied having these symptoms and 14 were uncertain, the last included most of the patients who were indifferent to a variable degree to all forms of stimuli. During the test (Metamucil) period 26 patients (65 per cent) were positive that they had no pain or distress and 14 (35 per cent) did not know. One, who had no pain during the control period, said he "feels better" after taking the preparation.

No increase in distention or tenderness was elicited in the second period during which the patients were receiving the psyllium mucilloid with dextrose.

Bleeding had been complained of by comparatively few subjects; the amount mentioned varying from a few streaks on the stool or paper to a "bowl full." None had reported bleeding after an evacuation. During the control period 5 admitted having bleeding, 21 denied it and 14 did not know. During the Metamucil or test period 1 patient reported a pronounced decrease in bleeding, 1 had slight bleeding following the removal of an adenoma with a biopsy punch, 24 reported no bleeding and the same 14 did not know. The patients who complained of leakage together with pain and distress

reported complete cessation of this symptom while taking the Metamucil.

EFFECTS IN DIABETES

Because of the dextrose content of Metamucil the advisability of its use by patients with diabetes was questioned, but to clarify this point the blood sugar values of 2 such hospitalized patients were determined during a control period of eleven days and for a similar time while the preparation was administered. The diabetic management during the two periods was not altered. During both periods blood was obtained before breakfast for fasting blood sugar determinations and again one hour after lunch. During the test period Metamucil was taken immediately after breakfast, lunch and dinner.

Fourteen blood sugar determinations were made during the control period and twenty in the test period. Calculations, however, were based on the same number in each period (Chart I). In the case of H.W. the fasting blood sugar for the control period averaged 169.43 mg., minimum 120 mg., and the afternoon blood sugar was 261.86 mg. with a minimum of 194 mg., while the respective figures during the test period were 157.14 and 225.85 mg with minimum readings of 114 and 166 mg. Similarly, in the case of M.S. the fasting blood sugars during the control period averaged 202.31 mg. while the afternoon average was 281.86 mg. compared with test period readings of 180.06 and 255.71 mg., respectively.

To expand the investigation 15 previously studied nondiabetic ambulatory patients and 1 with diabetes were selected and initial fasting blood sugar determinations were made daily for four days and then the patients were given Metamucil three times a day after meals for five days without other changes in diet or habits. During the test period fasting blood sugar determinations were rechecked and daily assays were made of the first morning specimen of urine. A total of thirty-two specimens of blood were thus tested; sixteen initially and sixteen during the test. The aggregate average initial blood sugar was 93.83 mg. and after five days of Metamucil it was 78.91 mg. Chart II shows a decline in the blood sugar values for every patient with the exception of the one with diabetes, M.S. in whom there was an increase. Previously however, this same patient had shown a decline in the blood sugar values with the use of Metamucil.

No attempt is being made to explain this phenomenon, but it is apparent that sugar levels are either not adversely altered as a result of consuming Metamucil over a period of time or are definitely lowered, thus its use in diabetes seems quite safe.

RENAL EFFECTS

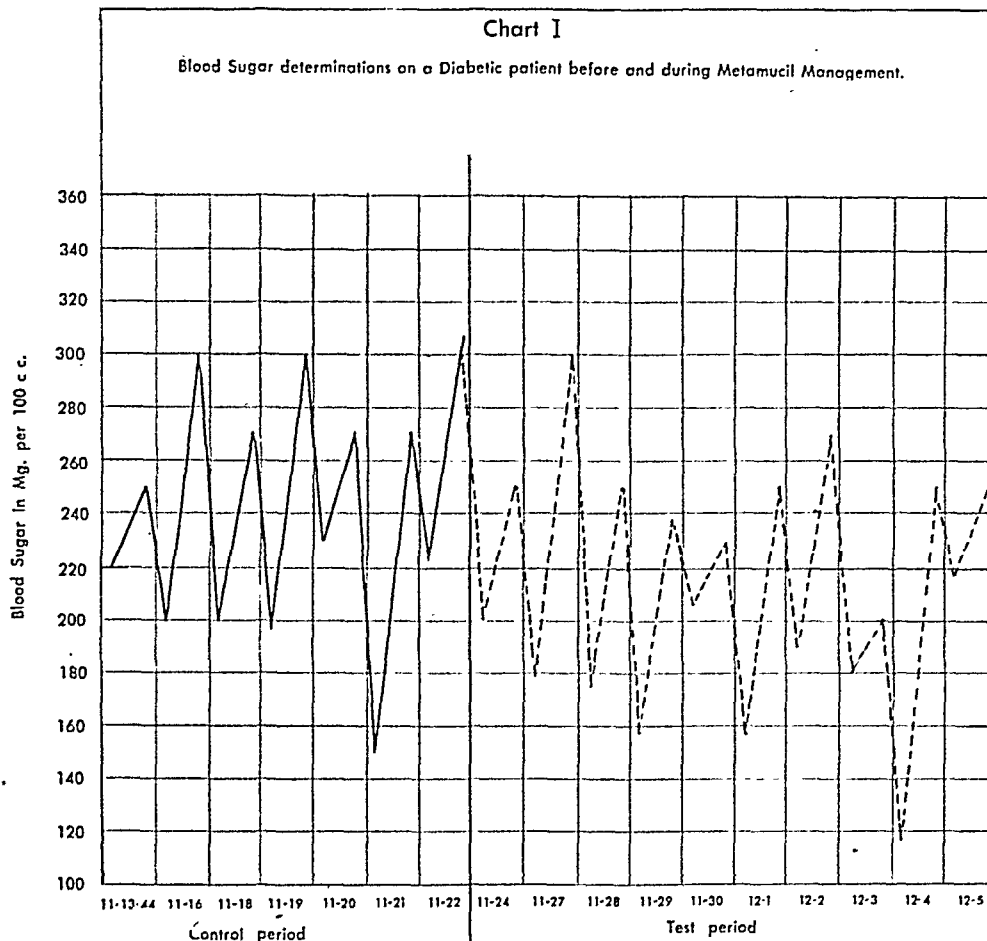
MacKay, Hall and Smith (10) reported that in albino rats fed ground psyllium seeds a black pigment developed throughout the renal cortex and

medulla, with microscopic granules in the tubular epithelium. This has not been established in human beings by autopsy, nor have there appeared any reports of clinical or laboratory evidence of renal damage attributable to the ingestion of the refined psyllium mucilloid.

Morning urine specimens of 16 subjects were chemically and microscopically examined daily for five days then these patients consumed Metamucil for five days and the daily analyses were repeated, making a total of 160 specimens examined. The acetic and nitric acid (Purdy's) tests were employed for the differentiation of albumin and mucin.

by employing twelve 10 grain tablets of barium sulfate, but the results were unsatisfactory due to difficulty in detecting their location. Then, as an experiment, we gave twelve tablets with the barium sulfate meal, only to find that they bunched together or piled up and, interestingly, progressed through the bowel less rapidly than the barium meal. Increased peristalsis was observed consistently throughout the entire series during the period of taking Metamucil.

We then adopted the following procedure: In the control phase of the study 1 ounce (30 cc.) of barium sulfate in a glass of water was administered to



Variable pathologic findings were present during both periods, but their frequency was no greater during the test as compared with the control period. Glycosuria present in the urine specimens of 2 patients disappeared entirely during the ingestion of Metamucil; the positive albumin test of 2 others during the control became negative during the test period. Urinary erythrocytes were present during the control period in three other specimens. These remained but were not increased during the test period. Thus, since pathologic findings did not increase it appears that the use of this type of preparation does not induce renal damage.

ROENTGENOLOGIC STUDIES

We attempted to eliminate the well known tendency of the barium meal to stimulate peristalsis

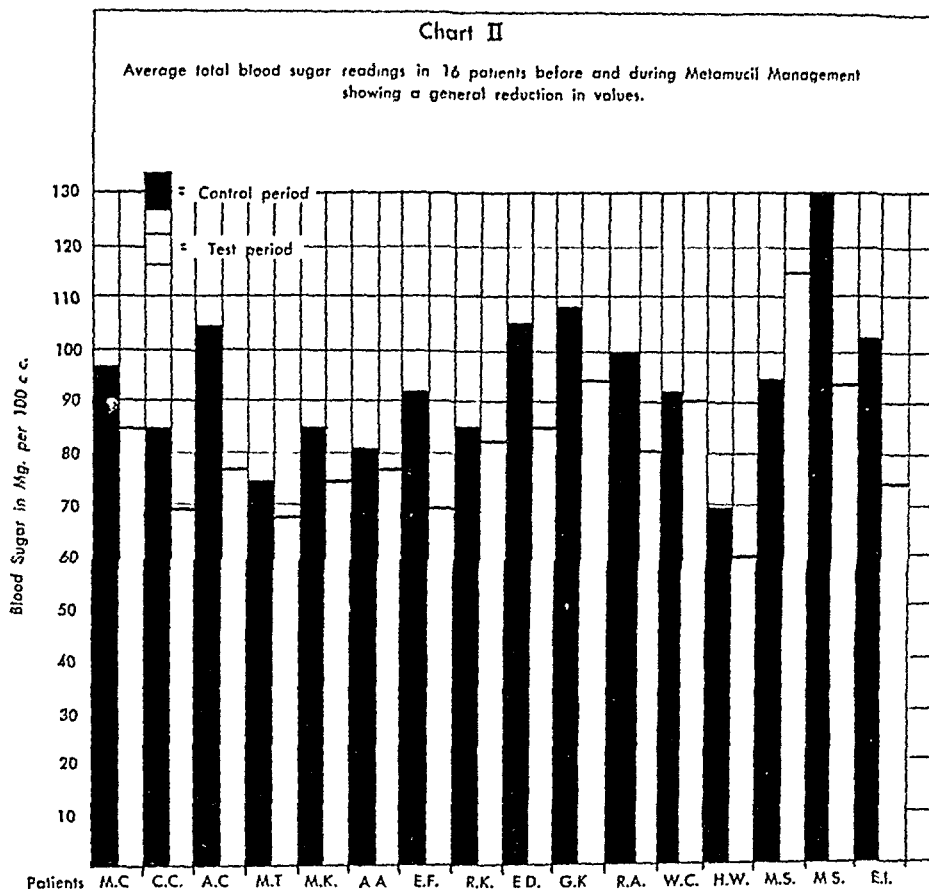
the fasting patient and the patient was fluoroscoped while drinking it. A film was then taken and repeated at hourly intervals for the first five hours and then every twenty-four hours until the barium was eliminated. A double contrast enema was then administered. In the test period the same procedure was carried out except that 8 ounces (240 cc.) of water containing one heaping teaspoonful of Metamucil was given one hour before the first film was taken. The patients continued to take the preparation three times a day after meals during the entire test period.

In this investigation 812 films of the gastrointestinal tract were taken; 437 during the control and 375 during the test period: For each patient in the control period a minimum of 7, a maximum of 19

or an average of 10.9 films were used, while the respective figures for the test period were 6, 20 and 9.87. Films taken in the control period ranged from 24 to 436 hours; in the test period from 24 to 504 hours. The prolonged emptying times did not occur in the same individual. Two patients became mentally disturbed and had to be excluded after having satisfactorily completed the control series.

Incidental roentgen findings were cholelithiasis in 1, a duodenal ulcer defect during both study periods in 1, diverticula of the sigmoid colon in 4, large bilateral renal calculi with pathologic urinary

emptying jejunum during the test period; the jejunum of 17 was empty, in 1 the meal had reached the splenic flexure and in 2 the jejunum was still full. During the control period the jejunum of 13 patients was empty, the column of barium had reached the hepatic flexure in 1 and in 1 the jejunum was still filled. In the control period after five hours the jejunum and ileum of 21 were full, the barium had reached the cecum in 1, the ascending colon in 8, the transverse colon in 2 and the splenic flexure in 2 as compared to 13 full, 5 empty, in 2 it had reached the cecum, in 6 the ascending colon,



findings during both periods in 1 and an hour-glass contraction of the stomach throughout the control period but absent after instituting Metamucil management in 1. Appendixes were demonstrated in 10 patients during the control and in 13 during the test period.

In Table I, showing the emptying time of the stomach, jejunum and ileum, it is seen that in practically every patient, during the test period, the stomach filled to a greater capacity because of the additional 8 ounces (240 cc.) of fluid taken, and yet the emptying time was shortened. In the control period 17 patients demonstrated a normal emptying time, 1 was very fast and 20 were delayed as compared to 18, 3 and 17, respectively, during the test period. Comparative films taken during the first five hours revealed a more rapidly

in 3 the hepatic flexure, in 1 the transverse colon and in 1 the sigmoid during the test period. The ileum of 12 after five hours during the control period was still full, while in 3 the meal had reached the cecum, in 1 the ascending colon, in 1 the hepatic flexure, in 1 the transverse colon and in 1 the splenic flexure as compared to 16 full, 2 filling, at the cecum in 1, at the ascending colon in 3, at the hepatic flexure in 5 and at the transverse colon in 3 during the test period.

In Table I it is shown that the emptying time of the stomach, jejunum and ileum was delayed during the control period. Although not pronounced it was consistent in all phases of the study, but it should be borne in mind that the subjects were selected because of their chronic constipation. During management with Metamucil there was a mod-

crate but quite definite increase in the rate of progress of the barium meal through the stomach and small intestine.

The colons of 5 patients were emptied in 48 hours during the control period, of 7 in 72 hours and of 3 in 96 hours as compared to 1 in 24 hours, 8 in 48 hours, 5 in 72 hours and 13 in 96 hours during the test period, a progress ratio of 2:1 (Table II). Even in those patients observed for as long as 168 hours we found that 32 had complete evacuations

omitted in 2 patients in the control period and in 3 in the test period due to lack of co-operation. The colons of 19 patients appeared quite normal during the control period as compared with 26 during the test period. Five cooperative patients were unable to retain the enema entirely and 4 partially during the test period while 2 of each type were encountered in the control phase. While on Metamucil an enlarged caliber of the colon was observed in 11 patients, with a definite increase in the dia-

TABLE I
Emptying Time and Progress of Barium Meal During Control and Test Periods

After Five Hours Stomach											
	Delayed	Normal	Fast								
Control Period	20	17	1								
Test Period	17	18	3								
After Five Hours Jejunum			Meal Progressed to								
	Empty	Full	Filling	Cecum	Ascending Colon	Hepatic Flexure	Trans. Colon	Splenic Flexure	Trans. Colon	Sigmoid	Total
Control Period	13	1				1					15
Test Period	17	2						1			20
After Five Hours Jejunum & Ileum			Meal Progressed to								
	Empty	Full	Filling	Cecum	Ascending Colon	Hepatic Flexure	Trans. Colon	Splenic Flexure	Trans. Colon	Sigmoid	Total
Control Period	0	21		1	8		2	2			34
Test Period	5	13		2	6	3	1			1	31
After Five Hours Ileum			Meal Progressed to								
	Empty	Full	Filling	Cecum	Ascending Colon	Hepatic Flexure	Trans. Colon	Splenic Flexure	Trans. Colon	Sigmoid	Total
Control Period		12		3	1	1	1	1			19
Test Period		16	2	1	3	5	3				30

during the test period as compared to 18 in the control period, still maintaining the same ratio of almost 2:1. Therefore the comparative study of the films discloses a definitely increased peristalsis during the period of Metamucil administration.

Table II also presents a record of those patients in whom the colon was NOT empty when the last film was taken. In the control period 12 had partially filled colons throughout 96 hours and 6 through 140 to 436 hours, but during the Metamucil management period the colons of only 5 were partially filled after 96 hours. However, in 2 of these 5 roentgen study was interrupted at 96 and 120 hours and in 2 after 48 hours. Thus a definite shortening of the colon emptying time resulted from the administration of Metamucil.

Double contrast barium enemas (Table III) were

meter and apparently in the length of the bowel. This probably could be attributed to spasmolysis if the same phenomenon had not occurred in patients who exhibited no bowel spasticity during the control studies. Spasticities, involving the sigmoid and transverse portions of the colon, were observed in 11 during the control period, but in only 5 during the test period. Atonicities of the bowel were noted in 2 and ptosis of the transverse colon in 8 during both phases of the study. Although none of the subjects complained of flatulence, some gaseous distention was observed in 11 during both periods.

LABORATORY AND PHYSICAL STUDIES

The stools of 15 cooperative hospitalized subjects were submitted daily for gross, microscopic

and bacteriologic examinations; the fifteenth patient was the obstipated employee who was able to furnish a specimen every second day only during the test period. The objective was to determine the effect of increased doses of Metamucil on the character, weight and bacterial counts of the stools.

Macroscopically, the stools during the control pe-

TABLE II
Colon Emptying Time

Hours	Control Period	Test Period	Case Number	Control Period Colon Not Empty at	Test Period Colon Empty at
24		1	3	315 hrs.	96 hrs.*
48	5	8	6	72 hrs.	48 hrs.
72	7	5	7	24 hrs.	48 hrs.
96	3	13	9	72 hrs.	48 hrs.
120	1	1	13	24 hrs.	24 hrs.
144	2	2	16	436 hrs.	120 hrs.*
168		2	18	48 hrs.	48 hrs.
192	2		19	96 hrs.	72 hrs.
240		1	20	192 hrs.	48 hrs.*
288	1		23	96 hrs.	96 hrs.
504		1	26	96 hrs.	72 hrs.
Total	21	34	27	316 hrs.	240 hrs.
			28	96 hrs.	48 hrs.*
			29	144 hrs.	168 hrs.
			36	96 hrs.	96 hrs.
			37	144 hrs.	96 hrs.
			40	220 hrs.	504 hrs.

*Bowel not empty at time shown. Further observations not possible.

TABLE III
Barium Enemas

	Negative	Partially Filled	Unable to Retain	Spasm	No Enema
Control Period	19	2	2	8	2
Test Period	26	4	5	2	3
Both Periods				3	

riod were semi-liquid, unformed, soft, formed, hard, contained undigested food particles, streaked with blood, and varied in color from a light brown to dark and yellowish green to green. During the test period the stools were spongy, rubbery, gelatinous, soft formed or putty-like; they were not streaked with blood and were usually tan, occasionally brown to dark brown, and rarely yellowish green.

A remarkable finding was that the fecal colon bacillus count was greatly decreased during the test period, despite an increase in the average weight and volume of residue, doubtless due to the added bulk supplied by Metamucil (Table IV). Specimens of one patient showed a definite increase in volume and weight and a decreased number of *Escherichia coli* when the dose of Metamucil was doubled. Suspecting a bacteriostatic effect of Metamucil, laboratory studies were done but in-vitro tests failed to confirm this.

Inspection of the anus and rectum during the control period revealed 17 to be normal, 2 untidy, 13 had skin tags, 3 rosets, 1 a sebaceous cyst, 3 anal fistulas, 2 vitiligo, 3 pruritus ani and 1 external thrombotic hemorrhoids. During the test period 19 were normal, none were untidy, none had external thrombotic hemorrhoids and the other lesions remained unchanged, thus function and hemorrhoids improved.

Digital anorectal examination during the control period revealed 14 subjects to be consistently normal, 14 exhibited spasm (4 painful), 5 were either spastic or normal and 7 were distinctly patulous and relaxed. During the test period 23 were consistently normal, only 5 exhibited spasm (3 painful), 6 were variable and 6 were patulous. Six patients had impactions during the control period, 4 complete and 2 partial, but no impactions occurred during the test observation.

Of the 174 sigmoidoscopic examinations performed 83 were in the control and 91 in the test period. These were of indispensable value in revealing consistent and characteristic changes in the appearance of the bowel and in the in-vivo stool induced by the ingestion of Metamucil. Two patients who became disturbed and uncooperative had to be excluded. The distance sigmoidoscoped ranged from 5 to 30 cm. Sigmoidoscopy of all patients as well as 6 with impaction was achieved with greater ease during the test period and distention was accomplished with much less air inflation. Fifteen patients presented evidence of internal and external hemorrhoids, papillitis and cryptitis and 5 had polyps. Ulcers or fissures of the anal canal were present in 8 patients in the control and in 7 during the test period.

The lower bowel was empty in 3 patients during the control period and in 8 while on Metamucil. During the control period the fecal residue present varied from hard-formed to mushy and mucoid and its appearance and consistency were inconstant. The odor was slight, moderate or foul. In 1 patient the lumen was partially filled with liquid petrolatum and the stool was brittle, hard and irregular, with many "cinder-like" fragments scattered throughout the oily film covering the mucosa—the typical liquid petrolatum stool. During the ingestion of Metamucil the stools were consistently and characteristically different: the masses were well formed, putty-like, smooth, round, usually light but sometimes dark brown and were dispersed in an orderly fashion throughout the bowel. There was no odor. The indifferent and untidy patients were entirely clean since the occurrence of the smooth "putty-like" stools and the more normal mucous membrane. Leakage previously experienced was absent.

A most striking feature was particularly noticeable during the test period: Within twenty-four hours after the ingestion of Metamucil definite changes began to manifest themselves in the bowel mucosa. Its appearance after two or more days

was most pronounced; that is, its color was light pink, the blood vessels were thin and normal and the surface was extremely clean, smooth and polished, as if it were "simonized." It might be moist, even slightly granular or show a follicular hyperplasia, but the clean, polished, glistening ("simonized") appearance persisted; this effect was more striking with the height of the sigmoidoscopic observation. Even the collapsed bowel seemed to be easily distended with much less air, the lumen appeared to be more dilated and fixed and the haustra in the sigmoid more numerous. There seemed to be a rather prominent fixation to the bowel that

tion were and remained normal throughout, codeine and aspirin were required to control pain. Theelin in oil, 5,000 units, was administered intramuscularly twice a week. On the day of admission she vomited a fetid dark brown liquid suggestive of fecal vomitus, this improved after a rectal tube was introduced but recurred two days later with abdominal pain, restlessness and chills. Fainting occurred following an unsuccessful soapsuds enema. The use of a colon tube brought relief after expulsion of a fetid liquid stool. Although on a liquid diet for one week she experienced three similar attacks. She was then placed on the routine general diet despite her complaints of flatulence and anorexia. After fifteen days without an evacuation she again had an attack of headache, vomiting and severe abdominal pain, relieved by a warm water enema. The stool was pasty and contained barium sulfate which was employed

TABLE IV
Escherichia Coli Counts

Case Number	1	2	5	6	9	13	17	20	23	26	28	32	34	37	38	
Control Period	Average Weight of Stool (grams)	41.4	94.2	30.7	72.7	77.8	43.6		32.8	45.0	24.6	59.1	22.2	59.6	34.7	87.1
	Average Esch. Coli Count	44.2	83.0	62.5	331.0	264.8	77.6		75.8	187.5	112.0	244.5	77.3	61.2	50.6	184.4
Test Period	Average Weight of Stool (grams)	12.9	102.5	36.8	25.8	35.8	70.6	44.8	20.5	143.4	25.7	92.3	57.7	68.9	71.6	122.2
								57.0		67.0						
	Average Esch. Coli Count	15.2	70.6	32.4	119.0	62.5	85.3	122.9	63.5	125.0	100.0	181.6	62.5	65.9	43.1	131.3
								2 drams 93.1		187.5						

gave one the impression that the progress of the peristaltic waves was favorably modified with the gradient increased decidedly downward. This may account for the difficulty experienced by some patients in retaining or even taking the barium enema.

CASE REPORT

Case No. 17—White, female, age 48, hospital attendant. She was admitted complaining of severe and protracted constipation, associated with dizziness, anorexia, distention, cramps, nausea with vomiting during the past week. She also complained of pain in the renal areas, a purulent vaginal discharge, edema of the ankles, nervousness and insomnia. Since childhood she had experienced evacuations at intervals of six to seven days and even then cathartics and/or enemas were required. For the past three years she had taken Hinkle pills twice a week supplemented by oils, enemas, massage and exercise in an effort to establish an evacuation habit, but even then, during and for some time following evacuation, there was sharp anorectal pain, bleeding, a mucous discharge, protrusion of internal hemorrhoids and occasionally swelling of the perianal tissues.

Physical examination was essentially normal except that the abdomen was distended but soft and tender throughout. The anal external sphincter was spastic, with a sentinel pile in the posterior midline. The blood pressure was 130/70.

By sigmoidoscopy the mucosa to 25 cm. was pink, slightly moist and granular with normal blood vessels and valves. The rectosigmoid appeared normal. The sigmoid was contracted with many haustra. There was an anal ulcer, papillitis and cryptitis, with external hemorrhoids 3 plus.

The specific gravity of the urine was 1.026, the albumin was 1 plus and there was an occasional pus cell. The blood count was normal; the fasting blood sugar was 54.5 mg. A scout film of the kidneys and a pyelogram were negative.

Hospital Course—Although the temperature and respira-

tion were and remained normal throughout, codeine and aspirin were required to control pain.

After the necessary measures to empty the bowel, the Metamucil test period was instituted. On the night of the second day there was considerable backache, followed by a spontaneous evacuation with complete relief the next morning. Two days later severe distention, pain and vomiting occurred and was relieved by a warm water enema. The Metamucil was then increased to 2 rounded teaspoonsful three times daily. This resulted in a decided improvement in her general condition and a spontaneous evacuation every two or three days. Except for mild cramps and flatulence at the beginning of the Metamucil regimen she had no complaints and was discharged greatly improved after a test period of three weeks.

During a follow-up of six months she stated that whenever she failed to take the Metamucil her condition became intolerable. A report seven months after her discharge stated that following gynecologic and rectal surgery severe obstipation recurred which necessitated the use of milk of magnesia, cascara and soapsuds enemas. With the permission of her attending physician she then used Metamucil and after increasing the dose to 3 teaspoonsful three times a day she had a copious evacuation within twenty-four hours. She says: "I am sorry I didn't report sooner. I gave myself a good tryout and just don't get along without Metamucil. I take it every day and have a thorough evacuation at least every third or fourth day."

DISCUSSION

Practically all of the previous work seems to be based on the theory that bulk is the dominant factor or influence in bowel evacuation. This theory, while tenable in some respects, seems to be devoid of actual proof. The reasons are obvious. The normal evacuation of the bowel is actuated by physi-

ologic processes consisting essentially of three major types of intestinal motion based on Cannon's (11) classic studies: rhythmic segmentation, peristalsis and pendulum movements. Rhythmic segmentation is due to a contraction of the circular muscle fibers, possibly occurring with a simultaneous relaxation of the longitudinal bands, and vice versa. Peristalsis is characterized by local relaxation of the tonus and rhythmic muscular contractions and inhibition below the point of stimulation, described by Bayliss and Starling (12) in 1898 as the "law of the intestines." Pendulum movements are annular constrictions which force the fecal mass out of one intestinal loop into another by a churning action without rhythmic segmentation.

Sollmann (13) states that the defecation reflex is started by the arrival of the mass in the rectum. It is greatly influenced, however, by the sensitiveness of the rectum and by the habits of the patient. It is here that the delay in evacuation principally occurs. A tonic mechanism for the rectum is located in the midbrain, and the rectal stretch reflexes are lost after low section of the medulla (Langworthy and Rosenberg [14]). Defecation usually involves a reflex through the spinal cord; but destruction of the lumbar and sacral cord results in diarrhea, lasting several days, followed by normal evacuation of the large intestine at the customary interval (Goltz and Ewald [15]). Therefore the defecation reflex, according to Schuller (16), can be controlled by the intrainstestinal mechanism if necessary. (For a review of the defecation reaction see Lehmann [71]).

Is it possible that this phenomenon can be attributed to the effect of bulk alone? Gray and Tainter (5) refer to the constipative effect of bulk produced by psyllium seeds (unprocessed). We (18) observed that the large, soft, spongy stool caused by banana ingestion can reduce activity and slow down peristalsis in patients with bacillary dysentery. In a study of fecal impactions often present in mental patients we observed a definite decrease in peristaltic waves and bowel activity until the accumulation of fecal matter became so great as to produce symptoms of obstruction. Further, it seemed most likely that the sudden increase in bowel activity, usually antiperistaltic, was due partly to some impairment in the circulation in the segment of bowel involved. Symptoms of antiperistalsis and obstruction due to prolonged obstipation occurred in one of the patients in the present series. Therefore it would seem that mere bulk is not the sole determining factor in the production of evacuation by these bulk-producing agents. A more potent factor or factors are implicated in this process.

Sollmann (13) classifies cathartic agents into four groups (determined on the basis of the action that they stimulate): (1) parasympathetic stimulants which produce intestinal spasm with toxic side actions and are not customarily used for cathartic therapy, (2) muscular stimulants which act directly on smooth muscle, (3) capillary poisons caused by specific toxins of various kinds and (4) mechanical

distenders which retain intestinal fluid and produce stools which vary from soft to copious watery evacuations, without inflammatory injury.

The preparation of processed psyllium seeds and dextrose (Metamucil) which we used not only produces a characteristic moderately bulky stool, but in addition, it possesses some chemical properties capable of producing consistent and sustained changes in the appearance of the bowel wall without the pigmentation attributable to some other cathartics. It is doubtful whether it exerts any action on the circulation of the bowel except that due to increased water absorption (interstitial absorption) and it appears to hold this liquid in a homogeneous suspension. It also absorbs residual moisture from the surface of the mucosa and probably from the circulating fluids in the bowel wall (parenteral absorption). This may account for the unusually clean, polished appearance of the mucosa and the somewhat fixed enlargement of the bowel lumen.

Undoubtedly the laxative properties of Metamucil meet the criteria expounded by Williams and Olmsted (19); namely, the impression of the patient as to whether or not the bowel movements were satisfactory and the weight of the feces over the weight of the residue recovered in the feces. Our patients, without prompting, mentioned the effectiveness of the preparation and the relief they experienced. None mentioned an increased urge or frequency of defecation, but stressed the amount expelled and the ease of expulsion. Nevertheless, the determination of effectiveness was not entirely dependent on subjective data as it was confirmed objectively by digital and sigmoidoscopic examinations. Moreover, frequent sigmoidoscopy afforded an accurate measurement of the content and motility of the distal bowel and through repeated digital examinations the function of the sphincteric apparatus was determined. Such procedures add much weight to the veracity of a patient's reaction to a particular experiment as the possibility of unintentional error is always great.

Ivy and Isaacs (8) show that the increase in bulk and moisture bears no relation to the quantity of bulk ingested or to the amount of water capable of being absorbed by a given amount of a gum; therefore some less direct factor must be involved in the production of bulk, probably a simple washing down of less fully digested food particles, such as proteins, or an increase in glandular activity with a resultant increase in cast off solids. Although gross weight only was considered throughout this study, a sufficient number of fecal specimens was obtained and compared to fulfil this particular requirement of the study. Gray and Tainter (5) maintain that the dry weight is not increased but there is an increase in the water content of the stool. Although the amount of food consumed by our subjects was weighed and measured so that it remained the same throughout the two periods, there was an increase in fecal bulk in a large majority of patients during the Metamucil period.

Furthermore, in the case of V.G. the bulk increased in proportion to the increasing doses of Metamucil administered. The appearance of the bowel wall, the round, smooth, homogeneous masses of residue and the absence of mucus or mucoid substances in the fecal mass would lead us to believe that the suggestion of protein washings is probably correct, but that of increased glandular activity is questionable. The tone of the bowel muscle is undoubtedly increased so that not only is the rectum and sigmoid evacuated completely but the patient is fully aware of an empty distal bowel.

Some patients found the first few doses of the mucilloid not very palatable, but it was unnecessary to alter its flavor in any instance because as they became aware of its value after the first few doses they insisted on its continued use after the study was completed. Although Gray and Tainter (5) emphasize the importance of ingesting large quantities of water not more than one additional glass of water, with each dose of the powder dissolved in a glass of water, was found necessary. A total intake of six glasses of water was a daily routine during the two periods under study; the fluid intake was observed as carefully as the food ingested in order to make a satisfactory comparison.

Abbott, Kair and Miller (20) report that the stomach and duodenum play a major role in the absorption of glucose, leaving only a scant fraction to be absorbed from the remaining portion of the gastrointestinal tract. They present evidence showing that as glucose enters the bowel, tonicity of the fluid is maintained by (1) a shift in the electrolyte content, (2) the absorption of glucose, (3) an inflow of hypotonic fluid and (4) a propulsive type of peristalsis which varies in intensity with hypertonicity. Thus the intestine is equipped with extremely effective mechanisms for disseminating and reducing the concentration of hypertonic fluids in the shortest possible time. Gauss (21) contends that the osmotic pressure of blood plasma does not satisfactorily explain the removal of glucose from the intestine. When concentrated glucose enters the bowel, fluid is poured into it to bring it to an osmotic equilibrium with the blood, and glucose enters the blood stream through the action of osmotic pressure. But when the concentration in the bowel is lower than in the blood, glucose continues to flow into the blood stream although opposed by osmotic pressure, and therefore forces other than diffusion through osmosis must be responsible. He believes that bile plays an important physiologic role in the mechanism of water balance. Despite the fact that Metamucil contains 50 per cent of dextrose blood sugar levels were consistently lower after its ingestion, even in diabetic patients. Moreover, patients showing evidence of glycosuria during the control were negative during the test period.

Any substance irritating to the bowel should produce characteristic changes. Laxatives, purgatives and hydragogues, when taken habitually over a period of time, will produce a thickened, granular,

usually dry and commonly a collapsed mucus membrane; cascara will often cause pigmentation (melanosis coli); the mucosa after a warm water enema appears pinker, brighter and flushed, but it becomes mildly to decidedly reddened and slightly edematous when soap or some other irritating substance is added. Liquid petrolatum keeps the lumen partially filled at all times; the mucosa can be seen to glisten through a film of oil, and when expelled the mucosa is typically granular, thickened and dry. Gray and Tainter (5) have suggested that the ground psyllium products break down to irritating end-products, which are incompletely absorbed and increase the water content as a result of the irritation. In our study no evidence of mucosal irritation was observed with the continuous ingestion of Metamucil. On the contrary, the mucosa appeared to be smooth, clean, pale pink and glistening. The effect seems to be one of stimulation rather than irritation. Sollmann (13) believes that the action of mucilaginous substances is emollient, mainly by retaining water in the intestine through imbibition, thus modifying the bulk and consistency of the feces so that they are more easily expelled, and that they are useful in habitual constipation by virtue of their demulcent action. Metamucil appears effective not only as a demulcent but also as a corrective in that it restores the normal water balance of the bowel.

SUMMARY AND CONCLUSIONS

An intensive and comparable study was conducted to determine the effect of Metamucil on the bowel and its contents, its clinical effectiveness and the occurrence of side reactions in 40 patients. The procedure consisted of a complete history, thorough physical examination, comprehensive blood and stool determinations, complete proctologic and roentgenologic studies during both the control and test periods.

Metamucil was found to be effective in both the atonic and spastic types of constipation, but more so in the latter.

Roentgenologic study disclosed that the gastrointestinal tract emptied more rapidly following the ingestion of Metamucil despite the increased volume of intake.

No untoward side reactions were observed. A most notable and distinct phenomenon, observed consistently, was the reduction in blood sugar levels and the absence of glycosuria in patients regularly consuming Metamucil during the test period. Patients reported relief of bowel and anal spasm, pain and tenesmus during the test period with Metamucil. This preparation produces a distinct and characteristic type of stool, a disappearance of fecal odor, a fixed and empty bowel, a smooth, highly glistening mucosa and an increase in the tone of the bowel musculature.

Metamucil is not habit forming or harmful and may be used over long periods of time without untoward effects.

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The Cause and Pathogenetic Mechanism of Hypertrophic Cirrhosis of the Liver of the Hanot Type

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ALL varieties of cirrhosis of the liver are forms of a chronic interstitial hepatitis.

PORTAL CIRRHOSIS

The most common form is widely known as alcoholic, portal, or Laennec's cirrhosis (⁸). It is characterized by (1) a clinically unrecognizable period of onset; (2) a state of general inanition of moderate or severe grade; (3) an initial enlargement of the liver followed by a later secondary diminution in size of the surface hobnail variety; (4) a wide spread variable hepatic cellular degeneration, especially of the fatty variety; (5) a normal lobular architecture; (6) a chronic progressive fibrosis of the interlobular septal stroma, so that bands of connective tissue surround one or more complete lobules; (7) atrophic constrictive destruction of the parenchymal cells beginning at the periphery of the lobule and progressing towards its center; (8) non-involvement of the intralobular connective tissue framework and the reticulo-endothelial system; (9) no demonstrable evidence of any acute inflammatory reaction or lymphatic enlargement; (10) late portal constrictive phenomena including relatively milder jaundice, ascites, and minimal enlargement of the spleen.

In portal, or perilobular cirrhosis, the outstanding

anatomical fact is that the fibrosis occurs in the interlobular septa and parallels accurately the lymphatic channels which occur there and there only. In the interior of the lobule, where there are no lymphatic vessels (Tobias ⁷), no fibrosis occurs. In a previous discussion of this subject (⁸) it seemed impossible to avoid the conclusion that the pathological progress was intimately associated, pathogenetically, with these lymphatic vessels, that a chronic intrahepatic lymphangitis was the essential cause of this form of cirrhosis, and that all the other assumed causes were associated and/or contributory causes and/or effects only.

HYPERTROPHIC CIRRHOSIS OF THE HANOT TYPE

The less common of these two groups of liver cirrhosis is commonly known as hypertrophic, or Hanot's cirrhosis and is the subject of this communication. Clinically, as considered in this communication, hypertrophic or Hanot's cirrhosis is characterized (1) by associated smooth surfaced enlargements of the liver and spleen without any subsequent contraction or other diminution in size of either organ; (2) by early continuous deep jaundice; and (3) by evidences of infection including (a) periodic exacerbations or crises with accompanying fever and leucocytosis, (b) further en-

largement of the spleen and lymph nodes, and (c) the occasional occurrence of peritonitis—all of this in the absence of any form of gross obstruction in the excretory liver duct system, and of constrictive obstruction in the portal venous bed.

In hypertrophic cirrhosis of the Hanot type, the gross appearances of the liver are characteristically different from those in the portal or Laennec form. The liver is the seat of a uniform excessive enlargement which lacks the hobnail appearance of the latter, and is smooth and unmarred to the touch and to sight. The enlargement is not that of a primary stage, as in portal cirrhosis; it is a continuous feature and persists throughout the course of the disease, and does not later at any time regress.

Microscopically, the outstanding fact is that the cirrhotic process is not only present in the interlobular septa, but that it penetrates the liver lobule. Bands of connective tissue fibers separate individual lobules in contradistinction to the much coarser and denser arrangement found in the multilobular form and in the portal variety. The fibrosis can then be traced as fine fibrillae which invade the interior of the liver lobule.

The connective tissue fibrillar fibrosis is somewhat like neuroglia, and has an open structure. It enters the lobules and surrounds single or groups of parenchymal cells. This is the characteristic feature of the Hanot type of cirrhosis (Kaufmann³), etc.). The fibrosis is much more intimately related to the interior of the lobules and to the individual cells. The fibrillar connective tissue contains branching elastic fibers which form a network between the cells and assume the characteristics of supporting framework.

The liver cords are characteristically fragmented into isolated and/or groups of parenchymal cells which seem entirely dissociated the one from the other. The disorganization of the normal lobular architecture is complete and the breaking up of the liver cords is distinct and is unique in pathology. As a consequence the sinusoids are recognized with difficulty or are frequently lost in the general disorientation and seem to have disappeared.

The liver cells are extremely well preserved and sometimes seem hypertrophied. They do not show the fatty and other degenerative changes that are seen in the Laennec type. The latter changes sometimes take place in the antemortem period. Nevertheless, the well preserved character of the liver parenchymal cells is a characteristic feature of this form of cirrhosis.

Small tubules of cubical cells are prominent in the connective tissue stroma; but these are not peculiar to this form of cirrhosis and are characteristic of any destructive lobular and/or parenchymal lesion. The small ducts show proliferation of their epithelial lining and the lumen is blocked by, or reduced in size by plugs of inspissated bile. The larger ducts show little, if any change. The minimal bile capillaries within the liver cords must be and are equally fragmented.

Evidences of an inflammatory reaction are present which, ordinarily, are not distinguishable in the portal or multilobular form of cirrhosis. Foci of suppuration

do not occur in contradistinction to their frequent presence in the biliary form of cirrhosis in which terminal duct obstruction is present as a characteristic feature.

In late cases, the process spreads outside of the lobules and into the interlobular stroma. Secondary multilobular cirrhosis then appears and complicates the picture. Mixed and atypical forms of cirrhosis are fairly common; only then is the microscopical picture confused and difficult of classification. In a well defined case, the anatomical picture is distinct, not to be mistaken and is a most remarkable one.

Enlargement of the spleen is a characteristic manifestation and is of major importance in hypertrophic cirrhosis. The splenic enlargement is definitely not an obstructive phenomenon. The splenic enlargement occurs early, in many cases demonstrably before any enlargement of the liver is detected. The splenomegaly is smooth surfaced, accompanies and matches the enlargement of the liver and frequently exceeds the latter. Microscopically, the stage of the process in the spleen may be more advanced than that in the liver. There is fibrosis, distention of the sinuses with blood and endothelial proliferation of the pulp. There is evidence of disruption of the terminal vascular channels and of the reticulo-endothelial framework of the splenic cords and pulp so that red blood cells escape from the former, break through the latter and spread throughout the splenic cellular structure. This contained mass of normal and abnormal blood and red blood cells contributes to the largest extent, if not entirely, to the total bulk of the spleen.

The third characteristic manifestation of hypertrophic cirrhosis of the liver is continuous jaundice. The icterus is not of a major gross—calculus or other—obstructive variety in the terminal bile ducts. In many cases, bile continues to discharge abundantly into the intestine and an increase in the bilirubin content of the bile is present.

The jaundice is associated with extraordinary splenic activity. In the spleen there are abundant evidences of vast blood destruction. Only those red blood cells are destroyed which leave the confines of the endothelial lined blood capillaries and sinuses. As indicated previously, blood escapes through the disrupted reticular structure into the splenic pulp. Red blood cells which circulate through the connective tissue framework of the spleen are ready for dissolution. Conversely, whenever splenectomy is followed by good results and the spleen is seen to be crowded with excess numbers of red blood cells, there are demonstrable severe vascular and reticulo-endothelial lesions in the spleen which permit the red blood cells to enter the pulp tissue. As a consequence, red blood cells in all stages of destruction and absorption are found throughout in intimate association with the macrophage cells of the reticulo-endothelial system of the spleen. In other words, changes are produced in the spleen in hypertrophic cirrhosis of the liver which produce the necessary conditions for a much increased red blood cell destruction. The destroyed blood cells are absorbed by phagocytic activity.

All of these evidences of blood destruction indicate strongly that hemolysis is the most important basis for the jaundice.

Difficulty in differentiating the rather uncommon Hanot type is common but should never be so. The biliary form is characterized by the following: (1) its appearance in much older individuals as against the occurrence of the Hanot type in younger individuals and even in children; (2) the much more frequent bouts of chills and fever in the biliary, than in the Hanot type; (3) the constant presence of obstructive pathology in the terminal duct system including usually, calculi and frank infection which is not present in the Hanot type; (4) the constant presence of foci of infection including multiple frank abscess in the liver parenchyma which is not present in the Hanot type; (5) the relatively lesser magnitude of enlargement of the spleen; (6) the absence of any degree of hemolysis in the spleen approaching that seen in the Hanot type; (7) the mixed forms of fibrosis which is commonly present in the biliary type, mostly resembling the interlobular type with minor fragmentation of the liver cords only at the peripheries of the lobules, so that typical pictures are obtained.

The microscopic picture is distinguished by its atypicalness. The tissue is characterized by scarring, jaundice, congestion and distortion of the architecture. There is breaking up of the lobule as in the Hanot type. Everything is irregular in distribution and follows the ducts. There is much evidence of inflammation. The liver cells are shrunken. The scarring is very irregular. Elements are seen which are present in both the portal and Hanot types.

DISCUSSION

In considering hypertrophic cirrhosis of the liver, certain common and apparently allied phenomena are striking; these include (1) the constant association of the liver, the spleen, the pancreas and their related lymph nodes; (2) the common involvement of the reticulo-endothelial system; and (3) the common blood supply through the mesenteric axis.

The association of the liver and spleen in hypertrophic cirrhosis has been emphasized in all the published communications as well as here. The fact that the pancreas undergoes similar fibrotic changes is apparently not so well known.

a. The pancreas.—In routine postmortem studies, pathological histological changes in pancreatic structure are frequent (Katsch and Brink from Askanazi's Institute⁽²⁾). Microscopically, there is a disseminated fibrosis; which is both interlobular and intralobular in distribution; there are scattered areas of small cell infiltration; and there is occasional intralobular oedema. The gland cells undergo fatty and pigmentary changes, but this does not affect the Langerhans cells.

b. The lymph nodes.—The lymph node changes are localized to the hepato-splenic-pancreatic area. In nearly all cases of hypertrophic cirrhosis, the lymph nodes are enlarged, dark in color, and oedematous. Microscopically, there are fibrosis and pigmentation. The

sinusoids are dilated and filled with polymorphonuclear and macrophage cells. The reticulo-endothelial network is hypertrophied. There are occasional foci of necrosis and hemorrhage.

c. The reticulo-endothelial system.—That part of the reticulo-endothelial system contained in the liver, the spleen, the pancreas and the associated lymph nodes seems to form an interdependent unit. The individual elements of the system include the finer framework of the liver lobules and of the splenic pulp and cords, the cells lining the sinusoids of the liver and spleen, the Kupfer cells of the liver, the histocytes of the loose connective tissue and of the circulating blood, and the splenocytes. Similar elements are found to a much less degree in the lymph nodes. The functional activity of the parts of this unit act in unison and are physiologically completely integrated.

1. *The liver.*—At the outer border of the lobule the connective tissue stroma penetrates the latter and assumes the character of the reticular tissue. The interior framework of the liver lobule is practically entirely a part of the reticulo-endothelial system.

In the liver, the sinusoids are lined by endothelial cells from which slender protoplasmic perivascular processes pass outwards into the perivascular space towards the hepatic cords. These processes are identical with the reticulum of lymph glands, and spleen and Mall⁽⁵⁾, definitely classifies them also as reticulum⁽¹⁻⁴⁾.

2. *The spleen.*—The finer framework of the spleen consists of reticular cells and fibers very delicately arranged in basket form. This framework also encircles the veins and is present in the Malpighian corpuscles. They are also found throughout the pulp and along the arteries where they form definite sheaths on the outside of the vessel wall, the so-called perithelium. This is not peculiar to the spleen.

In adult spleens the endothelium lining the vascular terminals is not a homogenous membrane. According to Mollier⁽⁶⁾ the wall consists of a reticular syncytium of endothelium with denser masses of protoplasm around the nuclei and with wide open meshes between.

The splenic tissue consists of the splenic pulp which fills all the spaces within the reticular framework of the organ and is arranged in anastomosing cylindrical cords; this constitutes the bulk of the spleen. Normally the pulp is composed of all types of cells which are generally found in the circulation, and, in addition, nongranular phagocytic reticular cells called splenocytes and macrophages are found. All of these bear the same relative relation to each other as is found in a lymph node. No lymphatic channels are present.

3. *The pancreas.*—Microscopically there is a disseminated fibrosis in the pancreas which spreads outwards from the blood vessels and from the duct structure. The characteristics and the interlobular and intralobular distribution of the fibrosis have such similarities to the character and to the distribution in the hepatic lesions as to indicate strongly that this part of the pancreatic framework is similar to the corresponding parts of the

liver and splenic framework and belongs to the reticulo-endothelial system.

4 *The lymph nodes.*—The reticulo-endothelial structure of the lymph nodes is well known. It resembles that in the spleen.

CONCLUSIONS

Certain deducible facts and conclusions stand out from this factual resume:

1. Hypertrophic cirrhosis of the liver of the Hanot type is not a disease of the liver, or of the spleen per se. Rather, it is a disease involving a group of related organs including the liver, the spleen, the pancreas, and associated lymph nodes. The facts point to the conclusion that the disease affects all of these organs simultaneously or consecutively in a variable sequence as a single essential process, and that it is probably associated with some inherent common factor, structure, or faculty, which is universally present in all of them.

2. The previous conclusion is supported by the distribution of the arterial blood supply to all of these organs from the mesenteric axis. There would therefore be no restriction as to which organ would be involved first, or whether more than one would be simultaneously affected. This corresponds with the clinical facts. In this disease, (1) either the spleen or the liver may recognizably antedate the other; and (2) the lesion may be much more advanced anatomically in either organ as compared with the other.

The conclusion seems inevitable that hypertrophic cirrhosis of the Hanot type is blood borne and ap-

proaches the area of disease through the mesenteric axis.

3. The microscopic anatomical picture indicates that in this disease, there is primary involvement of the mesoblastic connective tissue framework which has been differentiated as the reticulo-endothelial system.

It appears then that the disease known as hypertrophic cirrhosis of the Hanot type, is not a disease of the liver parenchyma, per se, or of the spleen pulp, per se, as ordinarily considered. Because the one common denominator of this whole business are the lesions of the elements of the reticulo-endothelial system, the disease is evidently essentially an equal affection of the reticulo-endothelial framework of all of these associated organs of a destructive and degenerative kind—a reticulo-endotheliolysis. The various diverse manifestations are due to the situation of the lesion in variously constructed organs such as the liver and the spleen with different functional manifestations. The symptoms, jaundice, etc., are due to changes in the structure and function of these organs, which are secondary to the essential reticulo-endothelial lesion.

The splenic picture indicates that the continuous jaundice which is such an important clinical feature of this disease is not a consequence of the liver pathology, but a hemolytic phenomenon entirely dependent upon the blood destruction in the spleen.

The abundant evidence of inflammatory change, the frequent clinical episodes of fever and other evidences of an infective process, and the occasional termination in a frank peritonitis, indicate that this is a haematogenous infection.

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Editorial

Organotherapy in Ulcerative Colitis, a New and Interesting Therapy

THERE ARE few gastro-intestinal conditions in which our present form of therapy is as unsatisfactory as in ulcerative colitis. There are only a few in which our medical knowledge is as limited as in this disease. Therefore, if any new conception is brought forward, we are bound to listen with the greatest interest.

A. Morton Gill reported some very interesting experiences at a meeting of the Royal Society of Medicine in London. He gave his patients with ulcerative colitis a preparation extracted from the mucosa of small intestines of pigs. One prepara-

tion, in which enzymal activity was retained, showed no effect. Another, more purified one, which contained defatted, desiccated mucosa, was very effective. As long as this preparation was taken the patient improved, but relapsed during those periods when no more capsules were available. The improvement appeared only after about three weeks therapy. Not all cases responded so favorably. It did not matter from which part of the small intestines the product was prepared. There was a minimum amount of the drug necessary; however, the results were not better by in-

creasing the dosage of the product over a certain amount.

These findings are of great importance, as Manson-Bahr immediately pointed out in the discussion. This experiment opens an entirely new field for further investigation.

From Gill's experiences we may deduce that ulcerative colitis is not an entity, and that the etiology is not always the same in all cases. His encouraging results point to the possibility that some deficiency caused by a certain factor or factors in the mucosa of the small intestines may be the cause of ulcerative colitis in a certain number of cases. Manson-Bahr in discussing this presentation said that he was always impressed by the similarity of mercurial poisoning and ulcerative colitis. He doubted that the new treatment would be effective in extremely toxic, fulminating cases of ulcerative colitis. It is our impression that the disease depletes the small intestines of some important factor which, when replaced, enables the patient to recover.

Clinically, ulcerative colitis behaves like an infectious disease. However, in spite of tremendous efforts, we have not been able to find the cause

with certainty. Many other ways of approach have been tried, but in vain. In spite of Gill's very valuable observations we are not entirely convinced that ulcerative colitis is caused by some deficiency in the mucosa of the small intestines. We rather suggest the explanation that, in the chronic stages, a deficiency in the small intestines develops, which, not being taken care of, prevents a healing of the pathology in the large intestines. However, as soon as the small intestinal deficiency is remedied by Gill's therapy, the colon is able to recover.

Organotherapy is still in its infancy. To our knowledge, it has been applied for the first time by Gill in ulcerative colitis. Even though he is not able to explain his success, this does not diminish the value of his work. It is important to watch his experiments and we hope that Gill's therapy will be checked and broadened by further investigations.

—Franz J. Lust,

REFERENCE

- A. Morton Gill: Treatment of Ulcerative Colitis with Intestinal Mucosa. Proceedings of the Royal Society of Medicine. Vol. 39, 9, 517. July 1946.

Book Reviews

Banting's Miracle. By Seale Harris, M. D., Pp. 245 (\$3.00), J. B. Lippincott Co., Philadelphia Pa., 1946.

Dr. Harris has written a faithful account of the life of the discoverer of insulin. The reviewer's authority springs from the fact that he was a classmate and life-long friend of Banting. Both Banting and Harris have been members of the Editorial Council of this Journal from its inception and the latter published his work on hyperinsulinism in its pages. I have been told how diligently Dr. Harris worked in Toronto, resurrecting the facts of Banting's life, a task made difficult by several considerations. There remained but a handful of Banting's intimate friends with whom he could talk, and most of them had been repeatedly interviewed by would-be biographers, all of whom have not as yet produced their books, (to date only one other has appeared,—*Sir Frederick Banting*, by Stevenson, Ryerson Press, Toronto). Certain phases of Banting's story are contained in papers which apparently have not, as yet, been opened to biographers, including certain aspects of his battle with medical authorities, his more intimate attitudes on religion and art, and his extensive commentaries on his visit to Russia. While Dr. Harris' book is smoothly written, it suffers, I think, by not having been written by himself, although he did all the research work. Yet the portrait of Banting as an individual is done without the least deviation from the facts, and for so small a book, it gives an adequate impression which will be well received both

by the profession and the public. Banting was a man of exceptional intellectual gifts and phenomenal will power, unspoiled by fame, devoted to science and his friends, unforgiving to those who obstructed him, filled with a refreshing enthusiasm for life, work and art, but, nevertheless, usually unhappy in his personal existence. The tragedy which he experienced at the time of the discovery of insulin is not overstated in this biography, and Banting often said that if it had been possible for him again to sink to such depths of despair, he would have been able to duplicate his insulin discovery in some other field.

Beaumont S. Cornell.

Science. By Douglas W. Hill, (\$2.75), Chemical Publishing Co., Brooklyn, N. Y., 1946.

As science progresses in its seven-league boots, there is no phase of human life which can escape its impact.

This book should be welcome to everyone who wants to profit by scientific progress and should be a guide in helping to decide what stand to take in the face of the newest overwhelming scientific developments. It is an optimistic, reassuring volume, explaining that there is no need to fear scientific discoveries, whether they concern an aircraft of incredible speed and almost infinite flying range, or the release of atomic power. The aim of science is to assist and not to destroy mankind.

Dr. Hill has been both an industrial and an aca-

demic scientist, having lived in Hitlerite Germany, England and the U. S. A., but here he is concerned with something much wider than the textbook conception of science. He gives a clear answer to those who argue that scientific progress is leading to man's destruction by showing that if the scientific method is applied in the "non-scientific" fields in religion, ethics, politics, education and leadership—man will learn how to use the technical inventions of science as stepping stones to social and economic progress.

The author believes science to mean the power to think logically, dispassionately, impersonally, objectively, and thoroughly, according to a definite pattern that can be consciously adopted and taught to extend knowledge by ordered experiment, and to act fearlessly in the conclusions reached.

The chief contribution that science and scientists have to make to the world's welfare has never been tried. This book is a plea and a challenge to that end.

The Decibel Notation. By V. V. L. RAO, Pp. 179, (\$3.75). Chemical Publishing Co. Brooklyn, New York.

This pioneering book is the first volume in the English language which explains in sufficient detail the origin, development and a wide range of applications of decibel notation with special reference to radio engineering and acoustics.

The subject has been developed from its principles assuming no high standard of mathematics on the part of the reader so that the average student of electrical engineering will not encounter any difficulty in understanding and applying the information given in the book. Many solved problems will prove most helpful to the radio and acoustics engineer and students.

The book is a masterly survey of the development of the logarithmic unit, zero levels and level signs, decibel meter and decibel graphs, sound levels and phon calculations, etc., which will be welcome to technical workers of the radio and acoustics field.

Abstracts of Current Literature

(Microfilm copies of papers may be obtained from the Medicofilm Service of the Army Medical Library at 25c per each complete article, not exceeding 25 pages in length—and 10c for each additional 10 pages or fraction thereof. Prepayment is not requested. Remittances may be made with subsequent orders and in such manner as found most convenient. Address—Medicofilm Service, Army Medical Library, Washington, D. C.)

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CLINICAL MEDICINE

BOWEL

SCHLOTTHAUR, H. L.: *Familial diverticulosis of colon: report of 7 cases in one family of 9 persons.* (Ann. Surg., v. 124, p. 497, Sept. 1946.)

A probable hereditary basis for diverticulosis was established in a family of nine siblings. The diverticulosis was found only in seven brothers: two sisters showed no evidence of diverticuli. Diagnoses were made from roentgenologic studies of the colon and the personal histories referring to gastrointestinal symptoms. —D. A. Wocher.

LICHTMAN, A. L.: *Malignant Lesions of the duodenum: a study of 49 cases.* Proceed. Meet. Mayo Clinic, v. 21, p. 473, Dec. 11, 1946.)

Carcinoma of the duodenum is rare even though it is an organ having a multiplicity of factors which are recognized as capable of influencing the development of carcinoma; chronic irritation, acid, alkali, enzymes, ulcerations, erosions, heterotopic tissue, etc. Cancer of the duodenum is found in about 33 per 100,000 necropsies as compared with 3,000 for

the stomach and comprises 0.3 per cent of intestinal carcinomas.

The author presents an analysis of 49 cases of malignant lesions of the duodenum. Lesions of the papilla of Vater were not included. Carcinoma was present in 44 cases, sarcomas in 2, leiomyosarcomas in 2, and lymphangio-endothelioma in one. The average age for the carcinoma patients was 55.4 years (ranging from the third to seventh decades); 30 were men and 14 women.

Obstructive features were common and predominant in 38 of the patients. In six patients the chief finding was anemia due to loss of blood. In 37 cases surgery (other than exploratory) for relief or cure was carried out with a hospital mortality rate of 21.6 per cent. When the obstruction was relieved by palliative surgery the progress of the lesion was frequently slow. While extension of the malignancy to local nodes may occur early, extension to distal points of importance, such as liver or lungs, is often a matter taking years. Consequently the author feels that surgery may be of real benefit in prolonging the patient's life, particularly if radical excision is carried out. —H. Stilyung.

LIVER AND GALLBLADDER

SHERLOCK, S., AND WALSH, V.: *Post-hepatitis syndrome*. (*Lancet*, v. 2, p. 482, Oct. 5, 1946.)

Following recovery from the clinical phase of acute hepatitis, there were found few signs of hepatic dysfunction in a group of 20 soldiers. The livers, however, were still enlarged and certain symptoms remained. Biopsy sections of the liver generally showed no abnormalities but some fatty changes and portal tract scarring were sometimes found. The syndrome could not be classified as that of post-hepatitis cirrhosis; possibly psychogenic factors may have been responsible for the symptoms. —E. J. Tallant.

SPAIN, D. M.: *Portal cirrhosis of the liver. Review of 250 necropsies with reference to sex differences*. (*Am. J. Clin. Pathol.*, v. 15, p. 215, 1946.)

In the series presented there were only 60 females as compared with 190 males. At death the average ages were 48.6 years for women, and 56.3 years for men. Chronic alcoholism was shown in the history of nearly all cases. Women died from the cirrhosis more frequently than the men; they also showed a higher incidence of jaundice and ascites. Esophageal varices were more predominant in incidence in the men. —G. Klenner.

ULCER

GRIMSON, K. S., TAYLOR, H. M., TRENT, J. C., WILSON, D. A., AND HILL, H. C.: *Effect of transthoracic vagotomy on functions of stomach of patients with peptic ulcer*. (*Southern Med. J.*, v. 39, p. 460, June, 1946.)

Ulcer symptoms were exhibited by 25 patients for periods varying from 3 to 35 years. All cases were refractory to medical management. The youngest patient at time of operation was 27 years old, the oldest 62 years. About 10 centimeters of each vagus trunk was resected within the chest and the esophageal nerve plexus excised. Because of retention or obstruction gastrojejunostomy or pyloroplasty was also performed in 5 of the 26 patients who were vagotomized. Four to 18 months after operation the patients showed no evidence of either ulcer or recurrence of ulcer. Ulcer pain was absent in all cases. Gastric motility and secretion were depressed in the fasting state. Apparently not only the psychic or reflex mechanism but also the chemical mechanism of gastric secretion is altered. The authors suggest that pyloroplasty or gastrojejunostomy be combined with bilateral vagotomy to give maximum benefits in certain cases, particularly in the presence of obstruction.

—D. A. Woche.

HUBACHER, O.: *Peptic ulcer treated with gastric and intestinal extracts*. (*Lancet*, v. 251, No. 6417, 1946.)

Gastric and intestinal extracts, lipoid and protein free, were made up using the water soluble fraction

for injection and the water insoluble fraction for oral administration in tablet form. Gastric and intestinal extracts were used for treatment of ulcer sites in their respective areas.

Of 54 cases of gastric and duodenal ulcers and other types of gastrointestinal complaint, only 3 patients were hospitalized or placed on a strict diet except that patients were told to avoid any foods causing symptoms. Patients were not absented from work. Most of the rest of the treatment consisted of 12 to 21 injections given daily or three times weekly, supplemented by tablets given 3 per day before meals or 6 per day, one tablet before and one tablet after meals, for several months. In especially resistant cases longer injection courses were given.

Decrease in subjective symptoms and in the size of the ulcer niche were used as criteria of improvement. With the exception of indurated ulcers and tumors, most cases showed clinical improvement with the majority of the 33 cases subjected to X-ray examination showing improved radiological appearance simultaneously. Two-thirds of the indurated ulcer cases showed clinical improvement, while less than half showed radiological improvement with the radiological structure rather than its size being the determining factor for suitability for treatment.

The treatment gave no undesirable side effects and took effect generally following the tenth injection or 14 days of treatment by tablet alone. Spring and autumn prophylactic treatment with abundant tablets may show promise, as the only cases (3) of relapse in 16 months were without this treatment.

—John Moffit.

ILLINGSWORTH, C. F. W., SCOTT, L. D. W., AND JAMIESON, R. A.: *Progress after perforated peptic ulcer*. (*Brit. Med. J.*, p. 787, 1946.)

A follow-up study was made on a series of 733 patients who had survived perforation of a peptic ulcer. All the patients had been hospitalized. Of the survivors that were traced 596 reappeared for re-examination. The cases were classified as being symptom-free, experiencing mild indigestion, or having a severe relapse. It was found that irrespective of the post-operative treatment (or medical treatment) the number of relapses increased with time. Because ulcers of the anterior wall are the ones that are more likely to perforate and the ulcer can penetrate only a short distance, before surgical intervention, it is obvious that a perforating ulcer usually is not a hopeless condition. Perforation of the posterior wall into the pancreas is rarer and healing is usually very difficult.

The older the ulcer before it perforated the poorer was the health of the patient following successful surgery. Older patients had better relief than younger patients. Factors such as habits, diet, occupation and psychology may have determined the post-operative healing differences between age

groups. In the group under study, reperforation, hemorrhage, or other conditions requiring surgery occurred in 20 per cent within 5 years. After 5 years 70 per cent of all the survivors had mild or severe relapse.
—F. E. St. George.

JAMIESON, R. A., ILLINGSWORTH, C. W. F., AND SCOTT, L. D. W.: *Tobacco ulcer dyspepsia*. (*Brit. Med. J.*, v. 2, p. 287, 1946.)

While peptic ulcer patients are generally advised to reduce their tobacco smoking, there has been no clear-cut study to show any correlation between the amount of smoking and the severity of the ulcer dyspepsia. The patients in this series had suffered acute perforation and were considered good test subjects. A total of 473 patients, ranging from 20 to 64 years of age, were studied. Included were light cigarette smokers, heavy cigarette smokers, and pipe smokers. Cigarette smokers had severe symptoms while pipe smokers had mild symptoms. While at first this appears to show a correlation between smoking and ulcer symptoms, statistical analysis proved otherwise. Symptoms in ulcer patients aged 50 to 64 years were milder than in younger ulcer patients. But the greatest cigarette smokers were found in the younger age group, and pipe smokers in the older age group. Consequently the relationship between smoking and ulcer symptoms probably was not one of cause and effect but a reflection of coincidental tobacco habits and age-ulcer symptom relationship. Furthermore, reducing the tobacco consumption had no effect on the severity of the ulcer symptoms of the patients who were smokers.
—F. E. St. George.

THERAPEUTICS

GOVAN, C. D., JR., AND DARROW, D. C.: *Potassium chloride in the dehydration of the diarrhea of infants*. (*J. Pediat.*, 28, 541, 1946.)

In cases of severe diarrhea of infants the dehydration is extensive and the loss of potassium from the body can be as high as 25 per cent of the estimated total potassium content. Replenishment of fluid is essential but potassium must also be given. The potassium is included in the sodium chloride-sodium lactate-glucose solution which is used parenterally. The potassium deficit is not accompanied by a corresponding loss of nitrogen or phosphorus, so that the potassium probably does not originate from the disintegration of the cells as a whole. The cells however may be damaged, with respect to certain functions as the result of diarrhea dehydration.

The authors formulate a plan of treatment too detailed and extensive for the present abstract. In a group of 53 infant patients treated by conventional methods 17 died, while in a group of 50 infants treated by the authors new method only 3 died. While mortality was reduced the duration or

intensity of the diarrhea was unaffected by the potassium. Two complications were noted: potassium intoxication with heart block and intense erythema with desquamation.
—N. M. Small.

LOVELADY, S. B., RAVDALI, L. M., AND HOSFELD, S. M.: *Levels of penicillin in the blood after the use in the vagina and rectum of suppositories containing penicillin calcium*. (*Proceed. Staff Meet. Mayo Clinic*, v. 21, p. 401, Oct. 1946.)

The oral dose of penicillin should be about five times the intramuscular dose, but in the patient with achlorhydria the intramuscular dose is effective. Suppositories containing 100,000 units of penicillin calcium were placed in the rectum of 33 patients. Blood levels of penicillin were determined 3 and 5 hours later. The rectal route was somewhat inferior to the vaginal route, presumably because of the inhibiting action of penicillinase produced by colon bacilli. However, in many patients enough penicillin was absorbed from the rectum in 3 to 5 hours to give significant blood penicillin levels.
—H. Stilyung.

SURGERY

WAUGH, J. M. AND CLAGETTA, O. T.: *Resection of duodenum and head of pancreas for carcinoma*. (*Surgery*, v. 20, p. 224, Aug. 1946.)

For carcinoma of the region of the ampulla of Vater the operation offering the greatest chance for cure is that involving resection of the duodenum and head of the pancreas. An operative mortality of 20 per cent attended 30 cases operated on at the Mayo Clinic. The two stage operation is preferable in the patient with liver damage. Pancreaticojejunostomy is desirable for maintaining post-operative nutritional balance. Choledochojejunostomy or cholecystojejunostomy is carried out, the latter preferably in the two-stage operation. The gastrojejunal anastomosis is made distal to the pancreatic and biliary anastomoses.
—B. R. Adolph, Jr.

YOUNG, J. P., AND COLE, W. H.: *Intraperitoneal administration of succinylsulfathiazole and phthalylsulfathiazole in peritonitis*. (*Arch. Surg.*, v. 53, p. 182, Aug. 1946.)

Implantation of succinylsulfathiazole or phthalylsulfathiazole in the peritoneal cavity leads to high blood concentrations of the drugs in four hours. The drugs are absorbed from the peritoneal cavity into the blood stream about as rapidly as sulfanilamide. In experiments on intraperitoneal implantation in both humans and dogs no temporary adhesions were noted. The low toxicities of both drugs makes it possible to use relatively high doses with safety.
—G. Klenner.

EXPERIMENTAL MEDICINE

PHYSIOLOGY

HOUSSAY, B. A., AND R. GERSCHMAN.: *Liberation and fixation of potassium by the intestine.* (*Rev. Soc. Argentina Biol.*, v. 19, No. 4, p. 359, 1943.)

Two types of experiments were made in dogs anesthetized with chloralose or nembutal: (a) loop of the small gut was grafted by anastomosis with the carotid artery and jugular vein; (b) the intestine was isolated by ligature of the aorta below the mesenteric artery, the celiac and the renal arteries were also tied; in some experiments the liver was removed. In the first case, potassium was determined in the carotid and jugular blood and measurement of the venous outflow were also made; in the second case, potassium was determined in the carotid, supraheptic, and portal blood. Potassium injected continuously for 10-45 minutes into the artery supplying the intestine, was retained until saturation occurred; when the injection was discontinued, potassium was liberated by the gut. Stimulation of the intestinal nerves, acetylcholine and eserine liberated potassium from the intestine; at the same time motility increased. Removal of the mucosa did not modify this effect. Asphyxia liberated potassium in small amounts from the intestine and in large quantities from the liver. Stimulation of the splanchnic nerves and adrenalin injections liberated potassium from the liver, but not from the intestine.

—Courtesy of Biological Abstracts.

MACLACHLAN, P. L.: *Effect of anoxic anoxia on gastric emptying time of rats fed corn oil.* (*Proceed. Soc. Exper. Biol. Med.*, v. 63, p. 147, Oct. 1946.)

Fat is absorbed to a lesser degree from the alimentary tract of rats kept at reduced partial pressures of oxygen than at atmospheric levels. Anoxic anoxia likewise has been shown to delay the emptying time of the stomach. In the present study it was found that the emptying of fat from the stomach was initially accelerated in animals kept at reduced oxygen tension. Therefore the decreased rate of absorption of fat in rats subjected to anoxic anoxia is not due to a prolonged gastric emptying.

—M. H. F. Friedman.

FRIESEN, S. R., BARONOFKY, I. D., AND WARGERSTEIN, O. H.: *Benadryl fails to protect against histamine-provoked ulcer.* (*Proceed. Soc. Exper. Biol. Med.*, v. 63, p. 23, Oct. 1946.)

Benadryl was found to be ineffective in altering the gastric secretory response to histamine in Pavlov and Heidenhain pouch dogs. This finding did not support that of Loew and co-workers who reported a 40 per cent inhibition in 3 out of 4 dogs. Seven healthy dogs were given daily intramuscular injections of histamine in beeswax and benadryl in

beeswax. The benadryl did not protect against the development of the histamine-provoked ulcers. The authors conclude that benadryl is not a specific histamine antagonist but counteracts only some of the histamine effects by its own pharmacologic action.

—M. H. F. Friedman.

FLAYER, M., AND JENNINGS, D.: *Fractional test meals on students awaiting examination results.* (*Lancet*, v. 251, No. 6419, 1946.)

In attempting to evaluate the relation of mental stress to gastrointestinal abnormality, Flayer and Jennings studied the effect of tension produced in 20 normal medical students awaiting examination results. Samples were taken at 20 minute intervals before and after announcement of examination results. All subjects had either no lunch or an early light carbohydrate meal.

There was no evidence of hypersecretion found even though tension before announcement of examination was artificially heightened by various means. No other abnormality could be found which could be ascribed to anxiety, depression, or elation either in the 16 who passed the exam or the 4 who failed it.

—John Moffit.

SHAY, H., KOMAROV, S. A., SIPLET, H., AND FELS, S. S.: *A gastric mucigogue action of the alkyl sulfates.* (*Science*, v. 103, p. 50, 1946.)

Anesthetized dogs with gastric fistula and the pylorus ligated were used. Sodium lauryl sulfate and sodium dodecyl sulfate were introduced into the stomach. When the gastric contents were subsequently drained they were found to contain mucin and chlorides. Some evidence of resorption from the gastric lumen was obtained. The secretion of mucin persisted for several hours after withdrawal of the stimulating agent and was not abolished by atropine.

—N. M. Small.

PATHOLOGY

GREEN, J., AND BRUNSCHWIG, A.: *Protective action of certain compounds against dietary hepatic damage in the rat.* (*Proceed. Soc. Exp. Biol. Med.* v. 61, p. 348, Apr. 1946.)

Rats of inbred strain were kept on a diet which previously had been found to result in varying degrees of fatty infiltration of the liver and cell necrosis, and if long maintained on the diet, in cirrhosis. The test supplements were added to the basic diet in such quantities that the sulfur of the -SH compounds were equivalent to the sulfur in 40 mg. of methionine. Both thioglycollic acid and glycollic acid afforded a certain degree of protection against hepatic cell necrosis but showed no lipotropic action. Apparently the factors responsible for hepatic fatty infiltration and parenchymal necrosis in dietary deficiency states are not identical.

—M. H. F. Friedman.

A Physical Symptom of Value in the Diagnosis of Gallbladder Pathology

By

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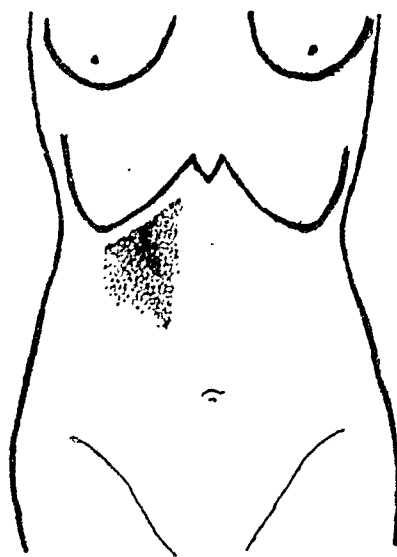
THE MOST important procedures in diagnosing affections of the gallbladder and bile ducts are the history, physical examinations, duodenal tube examinations, the x-ray and other laboratory aids (liver and pancreatic function tests, examinations of blood, urine and feces). Diagnosis is almost totally dependent upon these and by way of them a high percentage of accuracy in pointed or suggestive findings makes diagnosis possible. This article pertains strictly to a physical sign and does not consider further indirect symptoms of temperature, pulse, jaundice and abdominal distension. Records of this one finding have been kept in 400 gallbladder cases and matters pertaining to the elucidation of it are herewith presented.

THE FULLNESS SYMPTOM

At the onset it must be stated that this symptom should not be confused with definite contraction of the musculature occasionally seen in acute gallbladder cases or as it is more definitely noted in acute appendicitis or some instances of the gastroduodenal ulcer. Definitely it is not due to muscular contraction and may be best described as a faint degree of static fullness. It must also be presented that unless carefully searched for it is liable to be missed because it is a very delicate palpation symptom and requires the finesse of delicate palpation which seems never to be learned by some. Also, even with delicate fingers, it may require considerable experience before the ability of noting it is acquired. Since it is not uniformly present in all cases of gallbladder disease, and because it may be present at one time and not at another in the same case, its absence should not be taken in any conclusive negative sense. When present it has significance, when not present no negative clinical conclusions should be drawn.

After a considerable experience with it it was found that it is best elucidated with the patient flat on the back with the head slightly raised. The abdomen must be relaxed. When noted and to be sure of its presence, the left abdomen under the costal margin should be palpated the same way as the right side as a control and the two sides compared. The area in which it is noted is usually small not being more than three or four cm. in width or extension downward. In some instances the fullness may be diffused or irregular but usually it is a pyramidal shaped area with the base at or slightly below the costal margin and the apex pointing downward. Sometimes it is best noted by laying the hands one on each

side of the upper abdomen, the back of the hands being at the costal margins, the finger tips pointing to the ensiform, the hands sliding to and fro along the costal margins. If done in this way the examination may be concluded with the finger tips which latter may be all that is necessary. Graphically its location is as follows, the deeper shadows being the more common sites.



Areas where the fullness symptom is found the deeper shadow the most often.

It is best noted before deep palpation of the abdomen is engaged in. The degrees of pressure to note it is that of slight degrees, but little more than would be used to note Head zones or sensory skin phenomena. Its location may be anywhere from the ensiform to the flank depending upon whether one has a high or low gallbladder and apparently also the size of the organ. Since the vast majority of gallbladders occupy a site about midway between the ensiform and the flank, it is most often found in what is generally known to be the gallbladder region. It never occurs left of the center of the abdomen. The symptom is that of a fullness or a slight to moderate degree of static resistance directly below the costal margin on the right side.

Just what produces the symptom is not known. Perhaps it is due to a very mild degree of static contraction of the deepest fibres of the abdominal musculature overlaying the region of the gallbladder. Certainly it is not as easily palpable as muscular contraction such as is seen when definite inflammation of an underlying tissue exists. Often this physical finding is present when there are no other physical signs, and this is what gives it

paramount significance in clinical diagnosis, especially when it is remembered that in the average case of gallbladder pathology no physical symptoms are disclosed. Even tenderness noted by direct pressure on the median fissure of the liver where the gallbladder is situated may be absent when the symptom of fullness is definite. Most often though they both are present.

ITS PRESENCE IN ACUTE CHOLECYSTITIS

In the 51 cases of acute cholecystitis the definite and easily noted presence of muscle spasm was met with only fifteen times, whereas the symptom described was observed in twenty-two of the remaining thirty-six cases, the two making a total of the two of thirty-seven in fifty-one cases. It is interesting here that even in the instance of marked pathology, muscle guarding and the symptom of fullness described may not be present. It seemed probable that in some of the cases in which contraction or fullness were not present that the pathologic condition of the gallbladder was so rapid and acute that the sac was overwhelmed and deadened in that way not permitting these symptoms to develop. In seven of the negative cases gangrene of the gallbladder was present, and in two perforations of the gallbladder existed.

ITS PRESENCE IN CHRONIC CHOLECYSTITIS WITHOUT STONES

It is now believed that in the vast majority of instances of non-stone cholecystitis the condition is produced by chemical agents in the bile and that infection is a sequential or secondary matter. However, a gallbladder that has been damaged by chemical agents may become further deepened in its pathology by bacteria. The enormous ability of the gallbladder to absorb water from the bile exposes it to the escharotic action of concentrated bile salts and this with partial obstruction of the cystic duct (whether due to stones or edema) is the common cause of cholecystitis. We often see acute inflammation or great thickening of human gallbladder which contains no stones, but in the majority of instances (80 per cent) of human cholecystitis stones are present. The symptom then would tend to be present in the non-stone case according to the degree of edema, punctate hemorrhage, thickening of the gallbladder walls and cystic duct occlusion from congestion or edema. Since in the non-stone case these rarely exist or are very transitory, the symptom of fullness should not be depended upon to considerable numbers. While it may be absent when this gallbladder condition exists, at another time it may be positive and yet the case present no more clinical distress than in the first instance. This makes it important in all gallbladder cases not to decree its absence on the one examination but to feel for it several times during the course of a few weeks time. This is important because when it is definitely noticed its significance of a gallbladder pathology being present can be taken in a suggestive sense. No doubt this

irregularity is due to small degrees of cholecystitis that plays on and off, perhaps finally to become more steadily present, or just to continue in that moderate way over long periods of time. Occasionally it may be present for a short time after a heavy fat meal. When it is logical to assume that a chronic cholecystitis without stones exists, the symptom is such a more numerous finding in the gall stone cases that even with absence of findings of gall stones (cholecystography, duodenal drainage examinations), one should be suspicious that gall stones are present. In the cases in which stones are not diagnosable, the symptom would be present in only the minority of instances. Since such cases are best handled medically and only were operated upon in a few instances, there were only 81 in the group in which the diagnosis of chronic cholecystitis without stones was made, five having been operated upon. In these 81 cases the symptom of fullness was noted at the first instance or at some time in subsequent examinations in 34 or distinctly less than one-half.

CHRONIC CHOLECYSTITIS WITH STONES

In the remaining 268 cases of the 400 the symptomless gall stone and those with symptoms must be separated into two groups. Those in which gall stones were found in routine x-ray examinations and which were judged as symptomless so far as the distress from the gallbladder was concerned and in which other diagnoses were made were 39 in number and the symptom was present in only 11. This left 229 cases of Cholelithiasis cases with symptoms. As mentioned, gall stones were found in 42 of the 51 cases of acute cholecystitis, these are not included in this classification of chronic cases. The history of attacks of biliary colic, jaundice, persistent distress in the upper right abdomen or epigastrium was present in 174 cases. In the remaining 55 cases gallbladder pathology was suspected as the cause of a vague type of digestive distress in which an ana or sub gastric acidity was present in 36. In the 229 cases the symptom of fullness was present initially or at subsequent times in 174. Adding the eleven cases of "innocent gall stones" and the 22 of acute cholecystitis, the symptom described was present in 207 out of 400 cases, more than one-half.

This group of stone cases comprised by far the largest proportion and percentage in which the symptom was noted. The explanation I offer is that it is due probably to edema, hemorrhage or some degree of occlusion of the cystic duct which is more often present in the gall stone cases. These findings bring into significance the value of the symptom in what may be termed the most frequently met with gallbladder case clinically.

CONCLUSIONS

A new physical symptom for gallbladder diagnosis is presented, one that is of value when present, and one that is most often present in chronic cholecystitis with stones.

Hypertrophic Pyloric Stenosis in the Adult

By

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THE OCCURRENCE of hypertrophy of the pyloric muscle is not limited to infancy. Over one hundred cases have been reported in adults (1). Since Maier's paper in 1885 (2) describing the autopsy findings in 31 cases, the most extensive series has been that of Kirklin and Harris (3) which deals with the roentgen aspects of 81 cases. The belief that the condition is not rare, is corroborated by the appearance of two cases in hospital and private practice during a period of fourteen months.

The congenital form of hypertrophic pyloric stenosis may persist from infancy. Except for secondary gastric dilatation, it is usually unassociated with other lesions. This is an uncommon type. Crohn (4) was able to find only two cases which he felt were of congenital origin, and he added a case of his own. There is a second form which makes its initial appearance during adult life, and which is most usually associated with duodenal ulcer, gastric ulcer, gastritis or cholecystic disease.

ETIOLOGY

The etiology of the adult form of pyloric hypertrophy is not clear. In those cases in which there is no demonstrable disease near the pylorus, it is felt that an ulcer or gastritis might have initiated the hypertrophy and then undergone healing. When other lesions are present, it is difficult to ascertain whether they are primary or secondary.

Most observers believe that spasm, which is induced by autonomic dysfunction or other factors, is the basic cause of hypertrophic pyloric stenosis. Horton (5) found that there is a marked imbalance between the constrictor and dilator muscle fibers. Others hold that the condition is present from birth in a subclinical form, and the appearance of other disease near the pylorus causes progressive hypertrophy.

PATHOLOGY

The hypertrophied pylorus encroaches upon the pyloric lumen with the production of some degree of block. The process localizes itself to the valve producing a firm, circumscribed mass. Microscopically it appears primarily to involve the circular muscular layer, but it may involve the longitudinal layer as well. Such evidence of acute inflammation, which is found, is more likely due to the presence of an associated acute ulcer or gastritis than to the process itself.

SYMPTOMS

The congenital form gives rise to symptoms of pyloric obstruction of varying degrees from infancy.

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Retention vomiting is most characteristic. Other symptoms may arise from the presence of a secondary gastric dilatation.

Because the adult form of hypertrophy of the pylorus is so frequently associated with other gastroduodenal lesions, obstructive symptoms may appear in conjunction with symptoms of ulcer, gastritis or biliary tract disease. The patient may present with simple epigastric distress or an ulcer syndrome. Although obstructive symptoms are suggestive, there are no characteristic symptoms.

DIAGNOSIS

The preoperative diagnosis is difficult. Emaciation and anemia may be sufficiently pronounced in long standing cases of obstruction to suggest the existence of a malignant lesion. An epigastric mass may be palpable in a sufficiently thin patient. Gastric analysis reveals increased retention and a varying acidity. Kirklin and Harris (3) described certain x-ray features. They are: (1) Elongation of the pyloric ring; (2) Crescentic indentation of the base of the duodenal bulb; (3) Hyperperistalsis; (4) Gastric dilatation and retention. The gastroscope is of limited value in establishing a diagnosis because gastroscopic visualization of the pylorus is uncertain.

There are no absolute criteria for the diagnosis of hypertrophic pyloric stenosis. It can easily be mimicked by carcinoma of the stomach or masked by symptoms suggestive of an obstructing pyloric ulcer. Only by tissue examination can the exact diagnosis be determined.

Medical management is largely unsatisfactory because of the fixed mechanical barrier at the pylorus. However, a rigid medical regimen is indicated preoperatively for the control of the frequently coexistent gastroduodenal lesions and tissue edema.

The following two cases illustrate many of the clinical features of hypertrophic pyloric stenosis.

Case 1. C. H., a white male aged 34, was admitted to the Jewish Hospital on April 27, 1944 with a history of abdominal pain and vomiting during childhood, which ceased during his teens. Seven years prior to admission he had a return of abdominal distress, but had no actual pain until seven months before entering the hospital. Since then he had ulcer-like pain with partial relief from milk, but vomiting gave definite relief.

Physical examination was essentially negative.

The patient was placed on a rigid ulcer regimen, and the stomach was emptied twice daily. But his symptoms continued, and he had a morning gastric retention of as much as 240 cc.. He had a mild hyperacidity.

X-ray examination revealed canalization of the prepyloric portion of the stomach and a small irregularity

at the pyloro-duodenal junction, on the gastric side of the sphincter. There was some elongation of the pyloric canal, and a crescentic indentation at the base of the duodenal bulb was evident (Fig. 1). Approximately one-third of the barium meal was retained at the end of twenty-four hours.

The gastroscopist was unable to exclude a pyloric lesion.

At operation a firm mass was palpated at the pylorus. A subtotal gastric resection and gastrojejunostomy were performed.

Pathologic Examination-Gross: "The specimen consists of the distal portion of the stomach. The wall is smooth and flexible, except at the pylorus, where it is very firm and thickened. The mucosa is normal.



Fig. 1. Crescentic indentation of the base of the duodenal cap, and elongation of the pyloric canal. Note the prominence of the mucosal folds (Case 1).

Microscopic Examination: "The section shows slight thickening of the gastric mucosa. The submucosa and muscularis mucosa contain numerous lymphocytes and some plasma cells. The mucosa is intact. There is considerable hypertrophy of both the circular and longitudinal layers of muscle. A number of glands of Brunner are seen (Fig. 2).

"Pathologic Diagnosis: Hypertrophic pyloric stenosis."

This case represents the congenital variety of hypertrophic pyloric stenosis which persisted into adult life. Abdominal pain and vomiting had been present intermittently since childhood. Later the symptoms and x-ray appearance were suggestive of an obstructing ulcer, but pyloric muscle hypertrophy was the only lesion observed at operation.

Case 2. W. B., a 45-year-old housewife, had been having ulcer-like epigastric pain and retention vomiting for six years. She had nocturnal distress and experienced relief of pain from alkalis and milk. She had been a known hypertensive for six years.

Physical examination revealed an emaciated female of middle years. The blood pressure was 165/90. The heart was not enlarged. There was a small, firm mass in the mid-epigastrium which was slightly movable.

A moderate hypochromic anemia was present. Gastric analysis was normal. The stomach was repeatedly emptied, but no retention was noted.

X-ray examination revealed the presence of a ptosed stomach, the most dependent portion of which was three inches below the crest of ilium, with the patient in the prone position. The pyloric canal was elongated and eccentrically placed. A well-marked concavity was evident at the base of the duodenal bulb. (Fig. 3 and 4). At



Fig. 2. Hypertrophy of the pyloric muscle (Mag. 7x) (Case 1).

the end of twenty-four hours approximately twenty-five per cent of the barium meal was retained.

The patient was admitted to the Jewish Hospital where she was operated upon on July 10, 1945. At operation a firm mass was found in the region of the pylorus. Its nature could not be determined by gross examination. A subtotal gastrectomy and gastrojejunostomy were performed.

Pathologic Examination-Gross: "The specimen measures 16x6 cm.. In the center is an ulcerated area measuring 5.5 cm. in diameter, presenting numerous firm nodules the size of pin heads or larger, which cover the floor. The edge is raised. The mucosa near the ulcer is edematous.

"Microscopic Examination: There is a remarkable degree of inflammation and ulceration. The surface of the ulcerated areas is covered by polymorphonuclears and necrotic material. Inflammation extends into the submucosa, and there are areas of fibrosis and inflammation in the muscle. The submucosa is considerably thickened and edematous. The muscularis mucosa is extremely hypertrophied. There is hypertrophy of the circular and

longitudinal layers of muscle. A prominent feature is the amount of lymphoid tissue in the mucosa and the submucosa. The nodules which were seen grossly, consist of projections of mucosa with numbers of inflammatory cells in the connective tissue. In these projections the glands have been distorted, but most of them have not been destroyed. The sections were carefully examined for carcinoma, but none was found (Fig. 5).

Pathologic Diagnosis: 1. Severe follicular gastritis. 2. Benign hypertrophic pyloric stenosis."

A severe, localized hypertrophic gastritis was associated with hypertrophy of the pyloric muscle in this patient. The symptoms and course first suggested the presence of an obstructing ulcer. However, the discovery

preoperative diagnosis of an obstructing pyloric ulcer.

In a majority of the cases which appear during adult life, other lesions are found near the pylorus. The etiology of this type is obscure. Attempts to establish the sequential development of hypertrophy and the associated lesions from the history, were not successful in the second case. But it was not possible to exclude some degree of congenital hypertrophy.

The concavity at the base of the duodenal bulb described by Kirklin and Harris (3) is a suggestive x-ray sign. Bockus (1) states that a similar x-ray appearance may be produced by hypertrophic gastritis,



Fig. 3. Crescentic indentation of the base of the duodenal cap (Case 2).

of an epigastric mass and the presence of an anemia, made carcinoma the most likely preoperative diagnosis.

DISCUSSION

That the congenital type of pyloric hypertrophy can exist in the adult, without gross or microscopic evidence of other changes at the pylorus or the presence of other lesions near the pyloric sphincter, is illustrated by the first case. This type accounts for a smaller number of the cases which are encountered in the adult. It is of some interest to note that the patient was a male, the sex in which congenital hypertrophic stenosis occurs most frequently in infancy. When other lesions are present, they tend to modify the clinical appearance sufficiently to obscure the diagnosis. In the first case, where there was a history of vomiting since childhood, the x-ray demonstration of a small irregularity on the gastric side of the sphincter, favored a



Fig. 4. Elongated, eccentrically placed pyloric canal. Note prominence of gastric rugae.

pyloric ulcer, scirrhus carcinoma and other less common conditions. Both cases, especially the second, showed the crescentic deformity of the duodenal bulb. There was some elongation of the pyloric canal in both cases as well. Despite the x-ray configuration, other more common clinical possibilities obscured the preoperative diagnosis.

The pathologic diagnosis of pyloric muscle hypertrophy in the cases presented was based upon an examination of the sections by two pathologists. The sections were not cut in the manner described by Horwitz, Alvarez and Ascanio (6), which entails flattening the specimen on a piece of cork, and cutting longitudinal sections midway between the curvatures of the anterior wall. By employing that method they found the average thickness of the pylorus to be 5.8 ± 0.1 mm. It varied between 3.8 and 8.5 mm. Horton

(5) believes that one cannot determine the thickness of the pylorus since it varies with dilatation and contraction, and the age and size of the individual.

Spasm is invoked as the mechanism in many of the theories which attempt to explain the etiology of the adult type of pyloric stenosis. If this were the sole cause, one might expect those cases of long-standing pylorospasm to be followed by clinically manifest degrees of pyloric hypertrophy. However, there is no evidence that this relationship actually exists. It is

is too gross to ascertain the tone of the various components of the pyloric muscle. If there is a difference in tone between the muscle fibers, it is possible that that part of the musculature which will ultimately hypertrophy, may be in a state of dilatation. In other varieties of smooth muscle, such as the heart, hypertrophy follows dilatation rather than spasm (7). The same basic physiology must pertain to smooth muscle regardless of its situation, a fact which cannot be discarded in attempting to explain the hypertrophy of the pyloric muscle.

There would appear to be at least one other etiologic possibility in those cases of pyloric hypertrophy which occur in adult life. Thus far no observer can definitely exclude subclinical degrees of pyloric hypertrophy which may exist from birth. The fact is, the process does not occur with sufficient frequency in recorded series of ulcer and gastritis to regard it as a part of either process. Horwitz, Alvarez and Ascanio (6) found that duodenal ulcer, in the absence of obstruction, has little influence on the thickness of the muscle. They also found that gastric ulcer produces hypertrophy. However, it is quite possible that the disturbed gastric function resulting from some degree of congenital pyloric stenosis was a factor in the production of the gastric ulcers observed by them.

The diagnostic uncertainties, as well as the inadequacy of medical management in reversing a fixed pyloric obstruction, are indications for surgical intervention. Gastric resection combined with gastroenterostomy are to be preferred to a simple palliative operation, because of the frequent inability to differentiate the hypertrophied pyloric mass from malignancy.

CONCLUSIONS

1. Two cases of hypertrophic pyloric stenosis occurring in adults are presented. One case is of the congenital type. The second case was associated with a localized follicular gastritis.

2. The etiology of hypertrophic pyloric stenosis as it occurs in adults is discussed, and the possibility of causative factors in addition to simple spasm are mentioned.

3. The lack of absolute diagnostic criteria which would exclude other lesions, makes surgical operation and tissue examination necessary.

4. The condition is not rare in adults, and should be considered as a diagnostic possibility in pyloric obstruction.

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Fig. 5. Hypertrophied pyloric muscle (Mag. 7x). Note the confluent area of gastritis at the apex of the section which extends down to the submucosa (Case 2).

conceivable that continued spasm, operative with other factors, might combine to produce muscle hypertrophy in the adult. The diagnosis of spasm rests largely upon the x-ray appearance of the pylorus. Such a method

A Study of the Mortality Rate in a Series of Cholecystectomies

By

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THIS REVIEW of 558 cholecystectomies from the Surgical Service of the University of Kansas Hospitals covers a period from January 1, 1931, to July 1, 1946. It includes such additional operative procedures as choledochostomies, appendectomies, and an occasional duodenotomy, but does not include patients having cholecystectomy plus other major operations.

The influence of the following factors upon the mortality rate were studied:

1. Diagnosis
2. Age
3. Sex
4. Acute cholecystitis
5. Exploration of the common duct
6. Stones in the common duct
7. Jaundice
8. Cholecystectomy only
9. Cholecystectomy and choledochostomy
10. Cholecystectomy and appendectomy
11. Cholecystectomy, choledochostomy, and appendectomy
12. Preoperative preparation of the patient
13. Technic of the operation
14. Postoperative treatment
15. Causes of death

The diagnosis of gall tract disease with gall stones has usually not been difficult. The failure to recognize or to estimate the importance of such associated diseases as coronary sclerosis, myocarditis, chronic respiratory disease, kidney disease, and acute or chronic liver disease, has increased our mortality. In recent years almost every patient has had an X-ray examination. Those patients having symptoms of gall bladder disease with normal cholecystograms have been a constant diagnostic problem. When cholecystectomy has been done in such cases the results have been much less satisfactory than in patients who have had stones. Removal of the non-calculous gall bladder has not increased the death rate. Our experience substantiates the remark once made by Dr. George Crile, that "cholecystectomy is safest when the indication for it is least clear."

The ratio of males to females was approximately 1 to 5. The average age of males was 52.6 years and of females 48.1 years. The average age of males at death was 55 years and of females 52 years. The mortality of males was approximately 4 times that of females (Table I).

TABLE I
MORTALITY RATE IN MALES AND FEMALES
FOLLOWING CHOLECYSTECTOMY
(558) PATIENTS

Sex	Number of Patients	Percentage of Patients	Average Age	Average Age at Death	Number of Deaths	Percentage Mortality
Male	93	16.64	52.6	55	7	7.5†
Female	465	83.34	48.1	52	9	1.8†

The discussion concerning the optimum time to operate upon the acutely infected gall bladder still continues. Many able surgeons favor early cholecystectomy for acute cholecystitis, and equally as famous surgeons advise the waiting policy in most cases. In a recent study of "Cholecystitis with Perforation" Johnstone and Ostendorph (1) emphasize the danger of "so-called medical or conservative treatment of acute cholecystitis" and state that 49% of such cases resulted in perforation and death and were unrecognized and undiagnosed until necropsy. These authors further state that patients may be operated upon for acute cholecystitis within the first 48 hours with a mortality rate of 2.9%. Smith (2) expresses a more conservative attitude toward early operation for acute cholecystitis. He states that "individual pathological, local and systemic responses to gall bladder infection in a group of middle-aged or elderly persons does not have such uniform pattern that a simple surgical therapeutic rule can be applied to the group. Treatment must be individually rationalized."

In this series of 558 cholecystectomies two were operated upon within 48 hours of the onset of the symptoms. In addition there were 18 cholecystostomies for acute cholecystitis, two of which had perforated into the free peritoneal cavity. There were also 2 cases of acute perforation not operated upon and discovered at autopsy. Of the 4 cases of perforation, 3 died. There were 6 cases with pericholecystic abscess without a death. There were 2 deaths in the 10 remaining cases making a total number of deaths of 3 in 18 cholecystostomies, or 16.6% (Table II.) Cholecystostomy was done when the general condition of the patient did not seem to be favorable for a cholecystectomy.

When a patient enters the hospital with symptoms of acute cholecystitis it is our general policy to study the patient's condition for at least 24 hours. During that time the diagnosis can usually be established and the general condition of the patient determined. If the patient improves, the operation is postponed until symptoms of acute infection have subsided. If the patient grows worse, and the diagnosis seems clear, a cholecystostomy is advised. In other words, if an

TABLE II
CASES OF ACUTE CHOLECYSTITIS
TREATED WITH CHOLECYSTOSTOMY
(January 1, 1931 to July 1, 1946)

Gross Pathology	Number of Patients	Deaths	Mortality Rate
Acute Cholecystitis	10	2	20%
Acute Cholecystitis with pericholecystic abscess	6	0	0
Acute perforations	2	1	50%
Total Number of Cholecystostomies	18	3	16.6%
Acute perforations without operation	2	2	100%

emergency operation is done for acute cholecystitis, the operation of choice is cholecystostomy. In a very high percentage of patients the temperature drops to normal in a few days and a cholecystectomy may be done after the temperature has been at or near normal for five or more days.

The fact is recognized that cholecystectomy within the first 24 to 48 hours following the onset of acute symptoms of cholecystitis may be a logical and efficient treatment, but considerable education of physicians and patients will be necessary before a very large percentage of patients will reach the surgeon early. The further fact is just as clearly recognized that acute cholecystitis will subside in a very large percentage of cases if treated without operation. The relative safety of cholecystectomy after the acute infection of the gall bladder subsides cannot be disputed.

The death rate in cholecystectomy alone should not exceed 1 to 2 per cent. When choledochostomy is added the mortality is slightly increased (Table III). When stones are found in the common duct the mortality is greater than when stones are not found in the explored duct (Table IV). This is readily explained by the fact that when stones are present there is frequently jaundice and some liver damage (Table V). The addition of appendectomy probably does not increase the mortality rate. Appendectomy has usually not been done in this series when the general physical condition of the patient has not been good, when any acute infection existed in or about the gall bladder, or when the operation upon the gall tract was technically difficult (Table VI).

TABLE III
MORTALITY OF CHOLECYSTECTOMY
WITH AND WITHOUT
CHOLEDOCHOSTOMY

Cholecystectomy	Number Patients	Number Deaths	Percent Mortality
WITHOUT Choledochostomy	346	7	2.0%
With Choledochostomy	212	9	4.2%
TOTAL	558	16	2.8%

TABLE IV
CHOLEDOCHOSTOMIES IN 558 PATIENTS

Total number common ducts explored	212 — 38.1 %
Number in which stones were found	72 — 33.9%†
Percent of total number of patients (558) with stones	72 — 12.9%†
Number of deaths in group with stones	5 — 6.9%†
Number of deaths in group without stones	4 — 2.8%†

TABLE V
INFLUENCE OF JAUNDICE UPON MORTALITY

Total number of patients with jaundice	108 — 19.3%†
Death rate of patients with jaundice	4 — 3.7%†
Death rate of patients without jaundice (450)	12 — 2.6%†

TABLE VI
RELATION OF ADDED APPENDECTOMY TO DEATH RATE

Type of Operation	Number of Operations	Number of Deaths	Percent Mortality
Total operations	558	16	2.8%
Cholecystectomy only	198	4	2.0%
Cholecystectomy & Appendectomy	149	3	2.0%
Cholecystectomy Choledochostomy & Appendectomy	68	2	2.7%

The preoperative study and preparation of the patient is probably the greatest single factor in reducing mortality and morbidity in surgery of the gall tract. Since so many patients with disease of the biliary tract fall in the age group when respiratory, cardiovascular, renal and liver pathology are common it is imperative that all patients have, not only careful physical examinations, but such special examinations as X-ray, electrocardiographic, and liver and kidney function tests. When jaundice is present all patients have had prothrombin time studies and a careful estimation of the serum bilirubin, icterus index, urobilinogen and liver function tests to distinguish, when possible, between obstructive jaundice and hepatitis. Frequent consultations with the Medical Department, and particularly the cardiologist, have aided greatly in determining the optimum time for operation. Gastrointestinal X-ray studies have been made when the diagnosis was in doubt or when other disease was suspected. All jaundice cases receive Vitamin K. routinely. Transfusions are given before operation if the hemoglobin is below 70%. A routine gastric analysis is done. If there is no free hydrochloric acid in the stomach, acid is given as postoperative symptomatic treatment. The blood chemistry study includes non-protein nitrogen, sugar, chlorides and total cholesterol and the percentages of esters. In a few instances unsuspected kidney disease or diabetes has been discovered and treated before operation. The importance of sugar in the urine and an increased blood sugar is emphasized by Portis (3) in cases of liver damage. He describes such patients and warns that they should not all be considered dia-

betics. He explained the disturbance of sugar metabolism as due to a breakdown in the liver of glycogen to sugar faster than its storage. The administration of intravenous dextrose is indicated in such cases.

We believe that trained anaesthetists have contributed their part in lowering the mortality of gall bladder surgery in recent years. In a majority of our cases cyclopropane and ether have been used. In the past 8 months cyclopropane has been supplemented by the use of curare to obtain adequate relaxation in selected cases.

Infusions of 5% dextrose are given routinely during the operation. Transfusions have been given on the operating table when the hemoglobin was below normal, when the operation was difficult and prolonged, or when the possibility of shock was suspected.

Certain fundamental principles applicable to surgery of the gall tract have been followed. Good exposure is essential. Gall tract surgery cannot be done by the sense of touch. A good rule to follow is "visualize and identify everything before you cut anything."

The following routine operative procedures have been used in all cases unless technically impossible. They are (a) adequate incision for good exposure, (b) exposure and identification of the common hepatic, cystic, and common ducts, (c) careful identification of anomalies of ducts and blood vessels, (d) ligation of the cystic duct and the cystic artery separately, (e) aspiration of the common duct before opening its lumen, (f) exploration of ducts carefully to avoid unnecessary trauma, (g) exploration of ducts by palpation combined with scoop, probes, suction and irrigation, (h) testing of patency of papilla without forcibly dilating the papilla, (i) use of a T-tube for drainage of the common duct much smaller than the lumen of the duct to prevent injury by pressure after the duct is sutured, (j) use of a notched T-tube so that it may be withdrawn with a minimum of trauma, (k) injection of saline solution through the T-tube after closure of the wound in the common duct to test the patency of the opening into the duodenum, and to test for leakage along the suture line, (l) reduction of liver trauma to a minimum by careful dissection of the gall bladder bed, (m) suturing of omentum over the severed cystic duct and interposing omentum between the gall bladder bed and duodenum to reduce adhesions, (n) closure of the gall bladder bed with a continuous catgut suture, (o) placing the drain, when used, along the gall bladder bed to avoid contact with the ducts, (p) and careful closure of the wound to prevent disruption.

In cases of acute or subsiding acute cholecystitis, when structures are difficult to identify, the gall bladder has been removed from the fundus downward. In all other cases the gall bladder has been dissected out from the ducts to the fundus.

If there is any mucus in the air passages immediately following operation it is removed by suction by the anaesthetist. Bronchoscopy is done if atelectasis is suspected. An airway is left in place until the cough and swallowing reflexes have returned. Oxygen is given if there is any cyanosis or evidence of shock. Intra-

venous infusion of 5% dextrose is continued after operation. This infusion of dextrose with physiologic sodium chloride solution is continued daily to insure an intake of 3000 to 3500 cc of liquid. The total quantity of sodium chloride given should not exceed 5 to 9 grams daily. Transfusions are given if the hemoglobin drops or the illness is prolonged. Gastric suction is used if repeated vomiting occurs or if there is any evidence of acute dilatation of the stomach or ileus. Vitamin K is given routinely after the operation in all patients with jaundice. The sulphonamides and penicillin are given if infection is evident or suspected. If convalescence is prolonged and food cannot be taken by mouth, amigen is given daily to restore protein, and the intake of sodium chloride is reduced. Food is given by mouth as soon as it is tolerated. There is no such thing as a logical starvation period for all patients. The postoperative tolerance of the stomach should be the guide for food intake.

When the T-tube is removed from the seventh to the tenth postoperative day the cross arm of the T is cut off and the tube is reinserted along its tract and left in place for 48 hours, to afford good drainage and prevent "puddling" of bile about the common duct.

The patient is encouraged to breathe deeply and turn frequently in bed as soon as possible after operation. Very commonly the patient sits on the side of the bed or is up in a chair in from 3 to 5 days. Like the taking of food after operation, there is no set rule for getting the patient out of bed. Early rising and ambulation must depend upon the patient's general condition and not upon rule of thumb.

There were 16 deaths in this series of 558 cholecystectomies (Table VII). There were 15 autopsies. The causes of death are listed in Table VIII. There was such an imposing array of pathologic findings in most of the cases that it was very difficult to decide which disease caused death. Pneumonia in some degree was present in 6 cases but probably was the primary cause of death in but 1 case. There were 4 wound disruptions which may have been contributory factors in the death rate.

TABLE VII
MORTALITY RATE IN CHOLECYSTECTOMIES
IN 5 YEAR PERIODS
(Includes Choledochostomies,
Appendectomies, and Duodenotomies)

Time Period	Number of Operations	Number of Deaths	Percent Mortality
1931-1936	141	8	5.6†
1936-1941	186	7	3.7†
1941-1946	231	1	0.4†
Total			
1931-1946	558	16	2.8†

CAUSES OF DEATH

There was not a single death in this group that could be called an early "liver death" as described by Heyd (4). One patient dying 8 days after an operation might fall in Heyd's Group 3, which he describes as liver death

TABLE VIII
CAUSES OF DEATH

Bronchopneumonia	1
Acute dilatation of heart	5
Peritonitis	4
Acute and chronic Nephritis	1
Bile Peritonitis	1
Subphrenic and Subhepatic abscess	1
Acute toxic Hepatitis	2
Coronary occlusion	1
	<hr/> 16
In series were 4 wound disruptions, 1 hepato-renal syndrome, 1 tuberculous enteritis with perforation, 1 pituitary tumor, 15 autopsies.	

associated with renal degeneration of severe degree. The autopsy in this case showed acute hepatitis and toxic nephrosis. The blood non-protein-nitrogen rose to 214 before death. This case may be classified as one showing the hepatorenal syndrome.

SUMMARY

Our patients have been both private and charity of the type usually seen in a general hospital.

In a discussion of mortality rates it seems wise to separate patients into groups with comparable operations since such factors as choledochostomy, stones in the ducts, and jaundice influence the death rate.

It is quite apparent in literature reports that the question of early operation for acute cholecystitis has

not been definitely settled. We have followed the general plan of waiting for an acute infection of the gall bladder to subside and then do a cholecystectomy. In 18 patients with very acute infections cholecystostomy has been done. During the period covered by this study there have been 4 acute perforations of the gall bladder. Cholecystostomy has been the treatment of 2 of this number.

In our experience early cholecystectomy would hardly be rational since a large majority of our acute cases are several days old before they are seen by the surgeon. If early cholecystectomy in acute cholecystitis is to be the operation of choice patients must be seen by the surgeon within the first 48 hours after the onset of the acute attack.

In a discussion by Cole (5) in 1939 of the "Factors in the Prognosis and Mortality of Gall-Bladder Disease," he estimates that the mortality of operations upon the gall bladder as computed from numerous reports appears to be about 6.5 per cent. He also states that the mortality of choledochostomy throughout the country is probably no less than 10 per cent. These mortality percentages seem unnecessarily high when the advantages furnished by modern medicine and surgery are considered. Reduction in our mortality rate through the years has been due chiefly to improvement in preoperative preparation of the patient, surgical technique, and postoperative treatment. Skilled anaesthetists have contributed their part in reducing the death rate.

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Management of the Diabetic in Acute Infections and Surgical Emergencies

By

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WHEN THE literature relating to this subject is reviewed, each article seems to be introduced by the following statement—In the management of these conditions, close collaboration between the surgeon and the diabetic specialist is necessary. In this connection I should like to relate the experience at our hospital. Until 1931, surgical patients with diabetes were seen in consultation by the medical attending on service, often a man without special interest in diabetes. From 1931 on, I was asked to see and follow all the diabetics on the surgical service. This seemed to be a reasonably satisfactory arrangement and in 1938 I thought it would be interesting to go over the records and compare the effectiveness of diabetic management during the two periods. To my chagrin I found that during each of the periods there had been one death ascribable to diabetes and in each of these deaths overwhelming infection played a large part. It was further noted that many of the actual emergency situations were handled at the interne level and that diligence and interest made a very acceptable substitute for specialized knowledge.

Modern treatment of diabetes requires that the diabetic be taught as much as possible about his disease, thus giving him a measure of freedom which he could not otherwise enjoy. There seems to be no reason why the interested surgeon should not become informed regarding the principles of the handling of diabetics in surgical emergencies and thus avoid possible delay which might be dangerous to the patient and, perhaps less important, some of the awkwardness which frequently accompanies the dual management of a patient.

Diabetes has been characterized by Joslin as a state of insulin deficiency. This deficiency is of greater or lesser degree. We know that the deficiency is increased in the presence of infection. The mechanism of this increased deficiency in the presence of infection is not completely understood but it is probably not due to the inhibition of insulin formation or action. (1)

Best and Taylor elaborating on the question of the effect of infection, suggest that the decreased insulin content of the pancreas in certain severe infections does not necessarily indicate a decreased rate of liberation of insulin, that the suprarenals and thyroid glands are stimulated, that the synthesis of glycogen from lactic acid in the liver is inhibited and furthermore, normally liver glycogen is changed to glucose by phosphorylating mechanisms but in the presence of certain toxins an abnormal route of glycogen breakdown is provided which interferes with the action of insulin.

METABOLISM

In the non-diabetic individual in a normal state of nutrition, sufficient glycogen has been stored in the liver and muscles to provide carbohydrate for metabolic needs for approximately 36 hours of starvation. At the end of that time carbohydrate is obtained by the breakdown of protein. Ordinarily in starvation this is accomplished with sufficient rapidity, though at great expense in body protein, to prevent any severe degree of acidosis. As Stadie has shown, acidosis results when the metabolic demands are such as to require the oxidation of more than 200 grams of fat in each 24 hours. In states of severe insulin deficiency, requirements may go beyond this limit and acidosis result. For the purpose of reducing the level of fat catabolism, McKittrick and Root (5) many years ago advocated a minimum of 100 grams of CH per day for the surgical diabetic. More recently, Greene (6) has placed his minimum at 200 grams. It is at times comforting to know that the well controlled diabetic on a liberal CH intake comes to operation with a 24 hour supply of glycogen which he can draw on if circumstances make it wise not to administer CH by mouth or parenterally.

INSULIN

Soon after the advent of regular insulin, the Boston group popularized the method of giving doses of insulin based on the color obtained when the urine was tested at intervals with Benedict's qualitative solution. The amounts given were on the order of 15 to 20 units for a red or brown test; 10 units for yellow; 5 units for green. This method of administering insulin after the fact, as it were, has been very useful and the most practical devised until protamine zinc insulin came into wide use. This slow acting preparation has largely replaced regular insulin for the control of uncomplicated diabetes. As more experience has been gained with the new insulin its usefulness in the emergencies and the advantages of having a constant insulin supply made available have resulted in increased use of protamine zinc at least for partial coverage of the insulin requirement.

MANAGEMENT

For our present purposes diabetics will be divided into those previously under treatment for their diabetes and those whose diabetes has not previously been recognized. Each group can be further subdivided into diabetics in reasonably good control without infection; i. e., traumatic cases; diabetics with infection but still in good or reasonably good control; and diabetics with or without infection, in poor control or in acidosis.

*Read at a meeting of the New York Diabetic Ass'n. April 23, 1946.

The management of the known diabetic in reasonably good control and without infection presents no great problem. The usual daily dose of insulin may be given. However, if it is necessary to withhold food for more than 24 hours and the daily dose is 35 units or more of protamine insulin it is wiser to give $\frac{2}{3}$ of the usual dose. Urine specimens should be tested at frequent intervals and additional regular insulin given or not depending on the amount of glycosuria. When glucose is given parenterally each 50 grams should be covered by 25 units of regular insulin given at the same time.

If infection be present the insulin requirement will be unpredictably increased and the full daily dose in the form of protamine insulin should be given. Specimens should be tested at intervals of not more than 4 hours and additional doses of regular insulin given in amount depending on the spillage. During the period of infection it is useful and safe to give a daily dose of protamine insulin which approximates the total amount of insulin given during the previous 24 hours.

Due to the increased metabolism during infection, protein breakdown will be rapid and the protein sparing effects of CH given by mouth or parenterally should be utilized. It is useful in computing CH intake to remember that 100 cc of milk or a level teaspoon of sugar, taken in tea for instance, are each equivalent to 5 grams of CH, and 100 cc of orange juice, ginger ale or Coca Cola, are equivalent to 10 grams of CH. A daily intake of 100 to 200 grams of CH should be achieved if other considerations permit.

Should the diabetes be reasonably well controlled when the patient is first seen, necessary surgical procedures need not be delayed. In fact, promptness is advisable since drainage or removal of an infected area exerts such a beneficial effect on the severity of the diabetes.

Acidosis when present constitutes an emergency which demands consideration above all else. It should not be forgotten that severe acidosis with fever, leucocytosis, vomiting, abdominal pain, and other signs, may simulate the acute abdomen resulting in considerable confusion until these signs disappear as the acidosis is brought under control. Treatment should be vigorous, with the aim toward bringing the situation under control within 24 hours. Hydration must be achieved by the use of parenteral fluids, if necessary, though glucose is ordinarily withheld until the blood sugar level has been brought down to the normal range. It should also be remembered that a high renal threshold for sugar commonly exists in this condition and frequent blood sugar determinations may be necessary for the proper estimation of the situation, during the early stages of treatment. Since this is a condition of acute insulin deficiency, large doses of insulin will usually be required. To the adult, 50 units of protamine insulin and 50 units of regular insulin can be given immediately followed up by 25 to 50 units of regular insulin at 2 to 4 hour intervals as required by the level of the blood sugar and the degree of acidosis. Oliguria and anuria are ominous signs in acidosis but I know of no

specific measures other than those outlined above to combat them. The use of stimulants is not advocated. General measures, to be touched on later, should be used as the patient's condition indicates. However, if the patient is carefully followed and the principles outlined above applied, recovery is the rule, even with severe degrees of acidosis. Of course, this is primarily a medical emergency and would best be in the hands of one experienced in the handling of diabetes. It must be assumed that the uncontrolled diabetic has exhausted his glycogen stores and once control of the acidosis and hyperglycemia has been achieved, liberal amounts of CH should be given. Management then follows the plan previously outlined.

Let us now consider the patient whose diabetes has not previously been recognized. Should a patient, with or without infection, be facing a simple surgical procedure and a mild glycosuria and slight hyperglycemia—say in the neighborhood of 200 mgm—but without other diabetic symptoms, the procedure may be undertaken without delay. In fact the elimination of the injection may result in such a marked increase in glucose tolerance that the presence of diabetes may be difficult to demonstrate. However, should the diabetes be more severe and symptoms, such as polydipsia, polyuria, polyphagia, with weight loss, be present it is necessary to achieve some degree of control by the use of diet and insulin before proceeding. There is no magic method for determining the amount of insulin a diabetic will require but in general if the blood sugar is found to be between 200 and 300 mgm per cent he can be started on 25 units of protamine zinc insulin per day and adjustments made as necessary. If the fasting blood sugar is between 300 and 400 and acidosis is absent, a dose of between 35 and 50 units may be given. Should infection be present, this patient will require careful supervision and additional regular insulin will probably be required. Should the blood sugar be found to be above 400 mgm per cent some degree of acidosis will almost certainly be present and this phase of the problem must receive primary consideration. There is no contraindication to the use of penicillin and similar measures for the control of infection until surgical measures can be undertaken.

The patient with unrecognized diabetes who faces major elective surgery should receive a diet liberal in CH and protein and brought under control as soon as possible. When control is achieved, operation should be delayed 5 to 7 days to permit the patient to build up glycogen stores.

The presence of diabetes in his patient should not preoccupy the surgeon to the detriment of the total organism. Moderate degrees of glycosuria and hyperglycemia postoperatively are not detrimental. Greene (6) showed that delayed wound healing was not related to the height of the blood sugar but was rather a function of the blood supply. Many of the diabetic patients are elderly, with damaged vascular systems, slow hematopoiesis and poor general nutrition. These aspects should receive attention and whole blood, plasma, amino

acids and parenteral vitamins should generously though judiciously be used.

SUMMARY

To summarize then, it has been suggested that many of the surgical emergencies in the diabetic may be handled by the surgeon if certain fundamental principles of diabetic metabolism are recognized. Diabetes is a disease characterized by a state of insulin deficiency of greater or lesser degree and to avoid acidosis sufficient CH must be metabolized to avoid excessive catabolism of fat. The mild or well controlled diabetic satisfies the latter condition and therefore, minor pro-

cedures may be undertaken without further preparation. Infection in some manner not completely understood increases the insulin requirement of the diabetic and this must be taken into consideration in handling these conditions. Acidosis is a serious medical emergency and must be corrected before surgical intervention can be undertaken. Protamine zinc insulin has an important place in the treatment of acidosis in addition to its having largely replaced regular insulin in the management of the less severe surgical diabetic. And finally, the presence of diabetes in the patient should not permit us to overlook coexistent conditions which may, if not recognized, adversely affect the outcome for the diabetic patient facing a surgical emergency.

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Cancer of the Cecum A Review of the Clinical Features By

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MALIGNANCIES OF THE gastrointestinal tract rank high as a primary cause of death from cancer. Statistical reports during the past decade have revealed an apparently increasing incidence of such malignancies, which is attributed in some part to the increase in life expectancy and to improvement in diagnostic methods. Carcinoma of the cecum, which is estimated to comprise 6 to 20 per cent of malignancies of the large bowel, (38, 1) remains a difficult diagnostic problem despite its frequency. It is included in most reports only in a general discussion of cancer of the colon.

In a study of our patients with cancer originating in the cecum several points seemed worthy of emphasis. For this reason 50 cases from the literature and from the cases seen in the North Carolina Baptist Hospital were selected for review. The cases chosen were those which offered the most complete historical data and accessory laboratory studies prior to operation. The important diagnostic points are tabulated and reviewed.

REVIEW OF FINDINGS IN 50 INSTANCES OF CARCINOMA OF CECUM

Age and Sex

The average age of the patients was 47.8 years. Five patients were less than 30 years of age, the youngest

being 19. The oldest was 72 years of age. Sixty-six per cent of the patients were in the fourth to the seventh decade. The incidence was equally divided between males and females.

SYMPTOMS

The average duration of symptoms before operation was 10.1 months. The longest duration of symptoms was reported as 56 months. This patient had had an appendectomy performed five years previously, at which time a perforated appendix was found. Four months after operation a painless mass appeared at the operation site, and gradually increased in size. At the second operation, a resectable neoplasm involving the cecum and ascending colon was found.

Two other patients gave histories of vague gastrointestinal disturbances of several years' duration. In one, a carcinoid tumor of the cecum, with local and distant metastases, was found at necropsy. In the other, a carcinoid tumor of the cecum with metastases to adjacent lymph nodes was resected.

The symptoms described are listed in Table 2. No cases in which the symptoms could be attributed to an associated disorder are included in this review.

Pain was present in 92 per cent of the cases, and was the first indication of disease in 74 per cent. In almost all instances the pain was located in the right

TABLE 1

AGE	SEX		No. Cases	Per Cent of Cases
	M	F		
19-20	0	1	1	2.0
20-29	1	3	4	8.0
30-39	8	4	12	24.0
40-49	1	6	7	14.0
50-59	10	4	14	28.0
60-69	4	6	10	20.0
70-	1	1	2	4.0
TOTAL	25	25	50	100.0
AVERAGE AGE = 47.8 years				

TABLE 2

SYMPTOMS	No. Cases	Per Cent of Cases
Pain	46	92.0
Weight loss	23	46.0
Change in bowel habits	19	38.0
Weakness	12	24.0
Anorexia	10	20.0
Stool change	9	18.0
Abdominal distention	6	12.0
Vomiting	6	12.0
Mass	5	10.0
Anemia	4	8.0

lower quadrant. It usually began as a dull ache or soreness and progressed steadily until it became colicky in nature. No particular relationship to eating or to bowel habits were noted.

Weight loss was pronounced in 46 per cent. The amount of weight loss ranged from 8 to 55 pounds, the average being 25 pounds. The average duration of weight loss was 4.7 months.

Change in bowel habits was noted by 38 per cent of the patients. Constipation was noted by 8 persons and diarrhea by an equal number; only 2 patients reported constipation changing to diarrhea. Alternating episodes of constipation and diarrhea were present in only 1 instance.

Weakness and anorexia occurred in 24 and 20 per cent of the cases respectively, and accompanied the weight loss in practically every instance.

Change in the character of the stools was noted by 18 per cent of the patients. Twelve per cent noted tarry stools, 4 per cent decrease in the diameter of stools. Acholic stools were present in a jaundiced patient who was found at operation to have metastases to the liver.

Abdominal distention and vomiting were present in 12 per cent. Five patient (10 per cent) noted a mass in the right lower quadrant before they came for examination. In 2, it was the first indication of disease. The mass was present before operation for periods ranging from 1 to 56 months.

Anemia was the presenting complaint in 4 instances, and was the initial symptom in 2 patients. Prior to diagnosis all 4 had been treated with iron and injections of liver extract without response.

A family history of cancer of the colon was recorded in 2 instances.

SIGNS

TABLE 3

PHYSICAL FINDINGS	No. Cases	Per Cent of Cases
Mass	37	74.0
Tenderness Associated with Mass	17	34.0
Tenderness in R.L.Q. Without Mass	10	20.0
Normal Findings	3	6.0

A mass was palpable in 74 per cent of the patients, and was associated with tenderness in 34 per cent. In 20 per cent, tenderness was present in the right lower quadrant, but no mass was palpable. In 3 cases no abnormal physical findings were present.

ACCESSORY CLINICAL DATA

TABLE 4

ACCESSORY CLINICAL STUDIES	No. Cases	Average
Red cell count	22	3,700,000
Hemoglobin	23	63.5%
White cell count	24	11,760
Exam of stools for blood	15	
Positive	9	
Negative	6	
Barium enema	26	
Lesion demonstrated	25	
Normal findings	1	

The average red blood cell count as reported in 22 cases was 3,700,000. The lowest count was 1,500,000 and the highest 5,200,000. The average hemoglobin reading was 9.6 Gm., the lowest reading being 3.2 Gm. and the highest 13.5 Gm. The white blood cell count averaged 11,760 in 24 cases. The lowest count was 5,000 and the highest 21,000. A single stool examination for blood was positive in 60 per cent of the cases in which it was reported.

Radiologic examination proved to be the most valuable aid in diagnosis. Cecal lesions were demonstrated in 25 of the 26 cases in which barium enemas were done, and in most, the correct diagnosis was made pre-operatively. The usual findings were a filling defect and a change in the normal contour of the cecum. In 2 patients to whom a barium meal was given, the diagnosis was not made.

PREOPERATIVE CLINICAL DIAGNOSIS

TABLE 5

PREOPERATIVE DIAGNOSIS	No. Cases	Per Cent of Cases
Cancer of cecum	12	24.0
Acute appendicitis	5	10.0
Cancer of Asc. colon	3	6.0
Chronic appendicitis	2	4.0
Appendiceal abscess	2	4.0
Cancer of stomach	2	4.0
Tuberculosis of cecum	1	2.0
Ovarian cyst	1	2.0
Spathe colon	1	2.0
Not listed	21	42.0
TOTAL	50	100.0

The correct diagnosis of cancer of the cecum was made at the time of hospital admission in 12 of the 29 cases in which the clinical impression was recorded. Acute appendicitis was the diagnosis in 5 cases. (Two patients were found at operation to have appendicitis in addition to cancer of the cecum.) Cancer of the ascending colon was given as the admission diagnosis in 3 cases. The other diagnoses are seen in Table 5.

OPERATIVE FINDINGS

TABLE 6

OPERATIVE FINDINGS	No. Cases	Per Cent of Cases
Associated Pathology	10	20.0
Intussusception	5	10.0
Acute Appendicitis	2	4.0
Ruptured Appendix	1	2.0
Appendiceal Abscess	1	2.0
Colonic Diverticuli	1	2.0
Metastasis		
Regional	9	18.0
Distant	10	20.0

Other associated lesions were found at operation in 20 per cent of the cases. There were 5 instances of intussusception (10 per cent); 2 of acute appendicitis; 1 ruptured appendix; 1 appendiceal abscess, and 1 case of diverticulosis. Metastases were present in 38 per cent of the cases. In 5 of the 7 patients who had had previous appendectomies within a period of four months, regional or distant metastases were found at the time of operation.

DISCUSSION

A review of the data in 50 cases of cancer of the cecum reveals that in most instances the findings necessary for a tentative diagnosis of cancer of the cecum are present for many months before operation. The average duration of symptoms before diagnosis was ten months. Pain, usually located in the right lower quadrant, is the most outstanding symptom, and was the first indication of disease in three-fourths of the patients studied. Other predominant symptoms are weight loss, change in bowel habits, weakness, and anorexia. Both constipation and diarrhea occurred

frequently, but the alternation of constipation and diarrhea which is so often emphasized was present in only a single case.

On the basis of signs and symptoms, cancers of the cecum are usually divided into three groups:

1. The so-called dyspeptic group, characterized by indigestion, bloating, loss of appetite, and vague right lower quadrant discomfort.

2. Those causing refractory anemia without obvious blood loss.

3. Those instances where a mass in the right lower quadrant is the only indication of disease.

To these groups should be added cecal cancers producing the syndrome of appendicitis. In 7 of the cases reviewed, appendectomies had been performed within the preceding twelve months and had failed to relieve the presenting symptoms. In 4 of the 7 cases, changes attributed to secondary inflammation had been noted in the cecum at the time of the appendectomy.

The concomitant occurrence of acute appendicitis and cancer of the cecum is not uncommon. In several instances, acute, gangrenous, and ruptured appendices were found at the time of operation. The inadequacy of a "button hole" McBurney's incision in a middle-aged person with symptoms suggestive of appendicitis is obvious; the incision should allow adequate examination of the entire cecal area. No elderly patient should be dismissed with a diagnosis of "subsiding appendix" without further study. In the presence of right lower quadrant pain, a cecal tumor should always be suspected. Study of the colon by barium enema examination is the most valuable aid in diagnosis and should always be done. If this study is negative, and symptoms persist, a repeat examination should be performed in four to six weeks, especially if the stool remains positive for blood.

Of 221 patients with cancer of the cecum seen at the Mayo Clinic (22) between 1907 and 1928, resection was attempted in 145. Sixty lived five years or longer. In 15 of these, lymph nodes were involved. In 1939 Ransom reported 91 cases, of which 47.6 per cent were resectable (41). Invasion of regional lymph nodes was found in 44 per cent. In the present review, 10 of 19 patients who had resections were reported well at the end of eight to thirty-six months. It is impossible to predict the operability of the lesion from the case history. The relatively late occurrence of distant metastases and the good results in resections of the right half of the colon offer a favorable prognosis in most instances, provided the diagnosis is made within the first six months.

CONCLUSIONS

(1) Cancer of the cecum is estimated to comprise 6 to 20 per cent of carcinomas of the large bowel.

(2) A review of 50 case histories showed an average age of 47.8 years. The incidence was equal for males and females.

(3) The average duration of symptoms before operation was 10.1 months.

(4) The presenting symptoms in order of frequency

were pain, weight loss, the presence of a right lower quadrant mass, and moderate to marked anemia.

(5) Radiologic examination by barium enema is the most accurate aid in diagnosis.

(6) Cancer of the cecum may simulate acute or recurring appendicitis. When a history suggestive of appendicitis is obtained in middle-aged persons, adequate examination of the cecal region should be done

at the time of operation.

(7) Cecal carcinomas are slow-growing and only moderately invasive. Distant metastases occur comparatively late.

(8) Cancer of the cecum must always be considered in the differential diagnosis of right lower quadrant pain, a right lower quadrant mass, or severe unexplained anemia occurring in adults.

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An Evaluation of Some Antacid and Antipeptic Agents in the Prevention of Gastric Ulceration in the Rat

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WE (1) RECENTLY reported that gastric ulceration is produced in properly fasted rats if the spontaneously secreted gastric juice is allowed to accumulate in the stomach. We reported further that the determining factors were the presence in the stomach of an active gastric juice in large enough quantity and over a long enough period to produce the ulceration. We showed also that a direct relationship existed between the ulceration and the acid-pepsin content in the gastric juice. Under such experimental conditions, characteristic ulcerations developed regularly in the rumen, less often in the antrum, and least often in the body of the stomach. The gross and microscopic appearances of these lesions have been described. This regular development of ulcers, characteristic in appearance, in the rumen, itself devoid of any secretory cells, makes this experimental technique applicable to the study of many aspects of the ulcer problem. We have, in fact, ourselves, used it to assess the antipeptic action and certain other pharmacologic effects of Sodium Dodecyl Sulfate.

Pauls, Wick, and MacKay (2) have recently reported its application in the assay of the antiulcer principle in urine extracts. In the present study we have utilized this method to evaluate a number of agents already in common use, as well as some recently advocated, for the management of gastric and duodenal ulcers. Since the procedure also affords a satisfactory method for the quantitative study of gastric secretion, we have employed the rat's stomach as a "test tube in vivo" to appraise the action of the various agents upon this secretion. We hope these studies will also contribute to a better understanding of the long debated question of pepsin versus acid in the pathogenesis of ulcer.

METHODS

We used albino rats of Wistar strain grown in our own colony, housed singly in cages with raised wire bottoms of wide mesh. Animals weighing 180 grams or less were starved for 48 hours; those over 180 grams were starved for 72 hours. These periods of starvation were found necessary (1) to insure an empty stomach in the animal at the time of experimen-

tation. In spite of these rather long preparatory periods, 5 to 10% of the animals had to be discarded because of the quantity of food remaining in the stomach. Water was allowed *ad libitum* during the starvation period.

With the animal under initial light ether anesthesia, the abdomen was opened. The cecum was exposed and into it was injected 5% urethane (0.9 cc. per 100 grams body weight). The ether anesthesia was stopped and the small segment of the cecal wall around the needle puncture was exteriorized at the lower end of the abdominal incision as previously described (3). The pylorus was so tied as to avoid damage to the blood supply and traction upon it. The stomach was lavaged with 4 cc. of warm normal saline by injection and withdrawal, through an 8 French catheter used as a stomach tube. The volume of recovered lavage fluid was measured in order to get a minimum, 4 cc., recovery. If the lavage fluid was not reasonably clear, the animal was discarded.

When the stomach had been emptied of lavage fluid, 2 cc. of a 2% solution, or emulsion, of the test agent was instilled into the stomach through the catheter. In all the procedures, the catheter had to be removed and reinserted because the rat would not tolerate the catheter in place for more than 15 or 20 seconds without serious respiratory embarrassment. A smooth, gentle and rapid technique must be developed in order to achieve the best results. After gastric instillation of the test agent, the abdominal wall was closed by interrupted sutures. The abdominal wound was cleansed with normal saline, dried, and covered with a solution of collodion. These precautions usually prevent the rat from contaminating the gastric contents by licking the wound after the anesthetic wears off. Six hours after instillation of the test agent, the animals were deeply anesthetized by an intracecal injection of 1.2% Pentobarbital Sodium (0.5 cc. per 100 grams body weight). The abdomen was opened and a ligature placed around the esophagus, close to the diaphragm. The stomach was removed, inspected externally, and the contents drained into a graduated centrifuge tube through a nick in the stomach wall along the greater curvature adjacent to the pyloric ligature. The stomach was then opened along its greater curvature, stretched moderately by pinning on cork, and the inner surface examined with a dissecting binocular microscope, magnification 10.5x.

We chose 2 cc. of a 2% concentration of each reagent because from initial studies with aluminum hydroxide gel, under our experimental conditions, this amount was sufficient to give a high grade of protection to the rumen. We, therefore, adopted the same volume and concentration for the other agents to be tested. Further, we found that 2 cc. was the volume of fluid which could be routinely introduced into the stomach without causing regurgitation on removal of the catheter. Six hours were enough to yield a high incidence of rumen ulcers when 2 cc. normal saline were introduced into the stomach of control animals, without producing such advanced ulceration as to render the gastric contents useless for analysis as a result of contamination from bleeding or mucosal detritus.

ANALYSIS OF GASTRIC CONTENTS

The gastric contents of each stomach were analyzed individually and when the volume of contents permitted, we made the following determinations:

The specimens were centrifuged in a graduated centrifuge tube at 2000 revolutions per minute for 10 minutes. The volumes of supernatant and of solids were recorded. Rate of secretion was calculated from the volume of contents, less 2 cc.—the volume of test solution introduced into the stomach. The supernatant was pipetted off and the hydrogen ion concentration was determined with a Beckman pH meter and glass electrode. Free and total acid were titrated in the usual manner using Topfer's Solution and phenolphthalein as indicators and N/50 NaOH for titration. Total chlorides were determined through the method devised by Wilson and Ball (4).

Pepsin was determined with Mett tubes in two ways: (1) in undiluted gastric juice, (2) in juice diluted with fifteen volumes of 0.05 N HCl (5). In the first procedure determination was made on the unaltered contents as originally described by Mett (6). This result we have named "peptic activity," in contrast to "peptic concentration," which is determined by the second method under optimum conditions for peptic digestion. "Peptic concentration" represents the potential peptic power of the recovered contents and is a measure of the secretory activity of the peptic cells.

For the evaluation of the role of pepsin in the production of ulcers, "peptic activity" is more significant than "peptic concentration." We have rarely found "peptic activity" and "peptic concentration" of a gastric sample to be the same. This, in theory, should be the case if the pepsin present in the sample is capable of maximum digestion. "Peptic activity" was generally much lower than "peptic concentration," in spite of the presence often of an optimum pH for peptic digestion in the unaltered gastric contents. These results indicate the presence of peptic inhibitors in such contents.

DRUGS STUDIES

The untoward clinical effects which result from the indirect use of sodium bicarbonate and magnesium oxide as gastric antacids are well known. We have included them in the present study, nevertheless, be-

cause they have enjoyed so extended a period of almost exclusive use in the treatment of ulcer. Colloidal aluminum hydroxide ($\text{Al}_2(\text{OH})_6$), magnesium trisilicate ($\text{Mg}_2\text{Si}_3\text{O}_8$), sodium aluminum silicate ($\text{AlNaSi}_3\text{O}_8$), and the most recent addition to the group, di-basic aluminum aminoacetate ($\text{Al}(\text{OH})_2\text{OOCCH}_2\text{NH}_2$) are the newer antacids which were selected for study. The first three were included because they are the compounds most frequently used at present in ulcer therapy. Their relative merits have been discussed fully in the literature so that a review here is not necessary. (For an excellent summary of these see Bockus (7)). Krantz, Kibler and Bell (8) maintain that the addition of the aminoacid to the molecule would make aluminum hydroxide a more efficient antacid by giving it a dual effect: (1) immediate acid neutralization by the amino group, and (2) prolonged buffering of acid by the metathesis of the aluminum salt of amino acid and the strongly dissociated hydrochloric acid. In addition, they hold that such a compound through the resulting formation of aluminum chloride will exhibit the asstringency claimed for the ultimate action of aluminum hydroxide. In addition to their action as antacids, a property of diminishing "peptic activity" either by adsorption or by other mechanisms is ascribed to this group of compounds.

In Sodium Dodecyl Sulfate (hereafter referred to as SDS) we studied a representative of a third group, the alkyl sulfates, whose beneficial effects have hitherto been considered to be due to the inhibition of "peptic activity", with no effect upon acidity (9).

Water was used as the gastric instillate for a control series because practically all agents were studied either as water solutions or suspensions. Where a special vehicle such as methocel was used, a control group with this vehicle alone was included. Lastly, we studied the effects of normal saline, the results of which served as the base for comparison.

In evaluating the efficacy of the agents tested we have placed emphasis on the responses of experimental groups rather than on the results in the individual animal (Figures 1 and 2). Position in the charts of any group was determined by the degree of protection against ulceration afforded by the test substance. Greatest protection by single agents was afforded by colloidal aluminum hydroxide and by Sodium Dodecyl Sulfate. A mixture containing both was even more effective. The order of efficiency of the other agents was $\text{NaAlSi}_3\text{O}_8$, MgO , Di-basic aluminum aminoacetate in methocel $\text{Mg}_2\text{Si}_3\text{O}_8$, NaHCO_3 .
Groups with Saline, NaHCO_3 and H_2O

The greatest percentage of ulcerations was seen in the groups with saline (73%) and with NaHCO_3 (72%). The composition of the gastric contents was very similar in these two series and was characterized by low pH (1.41 and 1.46 respectively), relatively high acidity (73/51 and 57/46), high pepsin concentration (158 and 147 units), and "peptic activity" (16 and 18 units). The rates of secretion in the two groups were 0.37 cc. and 0.38 cc. per hour per 100 grams body weight. With distilled water ulcerations developed in

only 50% of the animals in spite of a greater rate of secretion (.51 cc.), a lower pH (1.24), a higher acidity (99/78), and a pepsin concentration equal to that obtained with saline but higher than that in the group

the volume of secretion; but the actual peptic power ("peptic activity") of the unaltered gastric contents. This conclusion is corroborated by other data in this study.

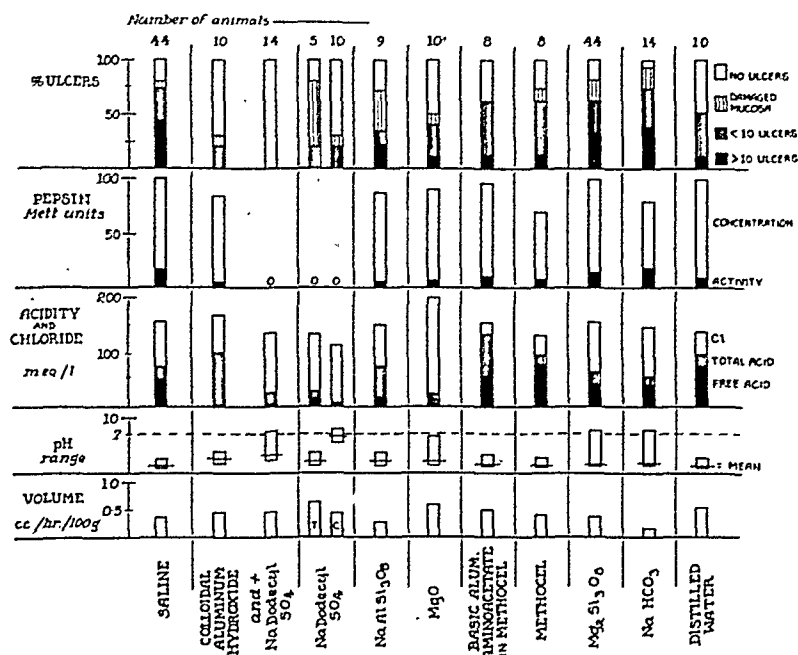


Fig. 1

C = Clear gastric contents
T = Turbid gastric contents

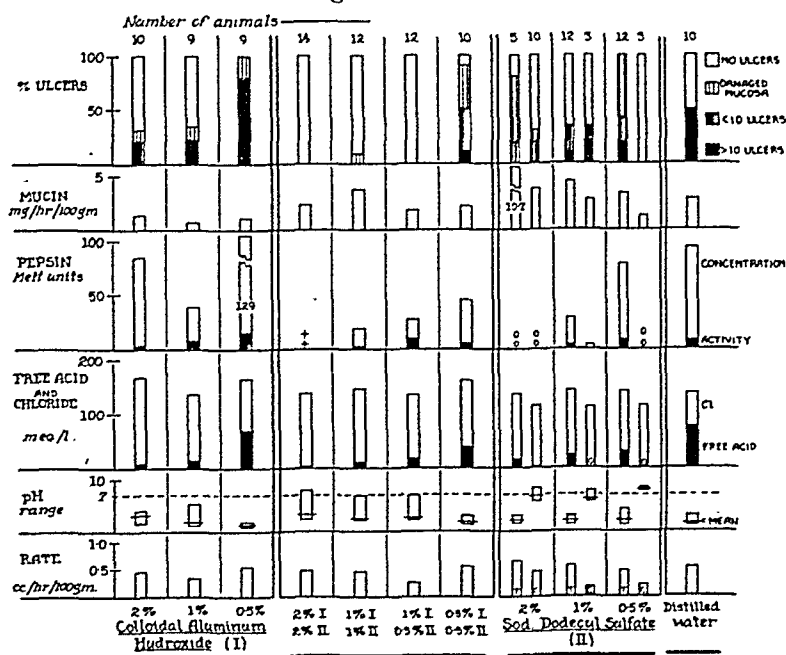


Fig. 2

C = Clear gastric contents
T = Turbid gastric contents

with NaHCO_3 . Only the "peptic activity" (13 units) was lower than that obtained in the animals instilled with saline (16 units), or with NaHCO_3 (18 units). These results indicate, that the determining factor in the formation of ulcerations was not the acidity, the potential peptic power ("pepsin concentration"), nor

RESULTS WITH OTHER AGENTS

The greatest protection against ulceration was obtained with a mixture of colloidal aluminum hydroxide and SDS. The gastric mucosa was normal in all the animals of the group in which we used the mixture.

The combination produced a high rate of secretion, a very low acidity, and practically no pepsin. Each of these agents used singly in 2% concentration was less effective than the mixture since only 80% of the animals in each group remained free of ulcers. Aluminum hydroxide produced a rate of secretion higher than that obtained with normal saline but less than that with water. Free acidity and "peptic activity" were very low, while total acidity and pepsin concentration were high. The high total acidity is not significant, since it represents, in large part, the buffer capacity of unaltered colloidal aluminum hydroxide and titration of the ionized aluminum chloride.

SDS produced two types of gastric contents (10), (11). In most animals of this group the recovered contents were clear and viscous with a high pH (6.43), a low acidity (9/1), and no pepsin. The rate of secretion was low (0.45 cc. per hour per 100 grams body weight) compared with the relatively high rate in the second type of response (0.65 cc. per hour per 100 grams body weight) in which the recovered gastric contents were turbid and much less viscous. This second type of contents had a low pH (2.17); a moderate acidity (29/15), and a pepsin concentration and activity of zero. The incidence of ulcers (20%) was equally low in both divisions of the group.

Since the two types of gastric contents which result from the use of SDS are discussed fully elsewhere (11), it is sufficient for our present purposes to mention that turbidity was present when parietal and peptic cell secretion occurred. The turbidity is due to the precipitation and inactivation of the pepsin by the SDS which takes place at a pH of less than 5.5 and is maximal at pH 2.5 (12). The clear samples had physical properties and gave chemical reactions typical for gastric mucus.

Sodium aluminum silicate ($\text{NaAlSi}_3\text{O}_8$) was next in order of efficacy in the prevention of ulceration. In the group treated with this agent, 35% of the animals showed ulceration in spite of a rather low pH (2.19) and high pepsin concentration (85 units) in the recovered gastric contents. Again, however, "peptic activity" was low (5 units). Magnesium oxide demonstrated protective qualities similar to those of sodium aluminum silicate. However, the beneficial effect of this agent seems to derive in part from dilution. The apparent rate of secretion was higher than for water and saline. But the exceedingly high chloride values (200 meq./l.) and very low acidity (23/12)—compare 78/11 for H_2O and 57/42 for NaHCO_3 —indicate that the increase in volume was not so much the result of the secretion of gastric juice as dilution by the tissue fluids diffused through the mucosa in response to the high (hypertonic) concentration of MgCl_2 derived from the neutralization of magnesium oxide by the hydrochloric acid of the gastric juice. Low incidence of ulcers (40%) again coincides with the rather low "peptic activity" (6 units) which prevailed in spite of a high concentration of pepsin (88 units).

The other compounds studied were much less effective in their protective action against ulcer forma-

tion. Each group in which di-basic aluminum aminoacetate in methocel, methocel alone, and magnesium trisilicate ($\text{Mg}_2\text{Si}_3\text{O}_8$) were used, showed an ulcer incidence of 62%. Since di-basic aluminum aminoacetate is insoluble in water we suspended it in methocel. From this standpoint the di-basic aluminum aminoacetate added nothing to the efficacy of methocel alone. On the contrary, this compound, under our experimental conditions, seemed to act as a secretory stimulant, since the rate of secretion, the acidity, and the pepsin concentration were considerably higher in this group than in the group treated with methocel.

Two conclusions are justified: (1) The most efficient antiulcer agents are a mixture of SDS and $\text{Al}_2(\text{OH})_6$. Next in order of efficacy is each of these agents used singly. (2) In all groups the development of ulceration exhibited a marked dependence on "peptic activity", while other variations in the gastric secretory response of the animals—rate of secretion, acidity, and pepsin concentration apparently did not influence the incidence of ulcers.

The infrequency of ulcers when SDS or colloidal aluminum hydroxide was used singly, and especially when combined, prompted us to attempt the determination of the minimal effective doses of the mixture. These results are presented in Fig. 2, which is self-explanatory.

We found that SDS in higher concentrations (about 2% in dogs (13) and rats (11)), has, in the majority of animals, a selective mucigogue action. This selective effect can also be found with lower concentrations of the alkyl sulfate, though much less frequently (Fig. 2) (clear samples (c)). Lower concentrations (0.1 to 0.5% in rats) usually stimulate the parietal and peptic cells as well. Stimulation of the mucous cells results largely from a direct cellular action, since it is only partially inhibited by atropine. Parietal and peptic cell stimulation is exclusively a vagus effect which is completely abolished by atropine (10), (11). Application of a 2% SDS to the stomach mucosa of the dog for a relatively short time (30 minutes) markedly reduces the secretory response to repeated doses of histamine (14). These facts must be considered in an interpretation of the findings in Fig. 2.

The effectiveness of SDS in the prevention of ulceration was striking in those stomachs which contained a clear viscous secretion. When the gastric contents were turbid protection was increasingly evident with increasing concentrations of SDS. These results are in keeping with the anti-peptic action reported for SDS *in vitro* (9). We found a 0.3% concentration of SDS *in vitro* able to inhibit completely a very active gastric juice.

Colloidal aluminum hydroxide in 2% concentration protected the rumen very effectively. The 0.5% concentration was very inefficient, since this group showed the highest incidence of ulcers (78%) in the entire study.

In combination, colloidal aluminum hydroxide and SDS appear to act synergistically in preventing ulceration, since a mixture of 1% of the former and

0.5% of the latter gave complete protection. SDS and colloidal aluminum hydroxide have desirable and undesirable local effects in the stomach. The desirable actions of SDS consist of an irreversible inactivation of pepsin by low concentrations of the agent *in vivo* as well as *in vitro* (15). Inhibition of this action of SDS by certain factors in food has, however, been reported (16). The mucigogue action of SDS which we (10), (11), (13) have reported has been observed with concentrations as low as 0.1% and is accelerated by increasing the concentration of the alkyl sulfate. Another possible salutary effect is the inhibition of parietal cell secretion, and perhaps of peptic cell activity. From a practical standpoint the stimulation of parietal and peptic cells by low concentrations of SDS is a distinct disadvantage for its use in the management of gastric and duodenal ulcer.

Colloidal aluminum hydroxide locally causes a relatively rapid lowering of acidity to pH 3.5 through its buffer action, if it is present in sufficient amount. Furthermore, it inhibits pepsin in the pH range of 1.0 to 7.0 and at pH 2.0 precipitates and inactivates it (17), (18). This agent also precipitates mucin, producing a rather firmly attached layer of precipitate to the mucosa. This precipitate was especially heavy over the antrum and was quite resistant to hydrochloric acid (19). Its disadvantages lie in the reversibility of pepsin inactivation. The pepsin precipitate dissolves readily in small amounts of hydrochloric acid with the liberation of very active pepsin (17). The local reactivation of highly concentrated accumulations of pepsin when acidity is still low, is, of course, undesirable; as a matter of fact, were such a precipitate to be reactivated in an ulcer crater, progression of the lesion toward perforation would be possible. We consider the reactivation of pepsin and precipitate following the use of the small amount of aluminum hydroxide in the 0.5% suspension, to be responsible for the inordinately high incidence of rumen ulcers in this group.

Aluminum chloride, the result of the interaction of aluminum hydroxide and hydrochloric acid in the stomach, has a marked astringent action. Whether or not this is beneficial is a matter of opinion. If prolonged, such an action can be irritating. Since our results indicate that relatively large amounts of aluminum hydroxide may be necessary for its most effective action, the possibility of an irritative effect should be considered.

Our studies indicate that a distinct advantage might be gained in combining colloidal aluminum hydroxide and SDS in therapy. The instantaneous and irreversible inactivation of pepsin by SDS would remove the most objectionable feature of the aluminum hydroxide. On the other hand, aluminum hydroxide enhances the beneficial mucigogue action of SDS by precipitating the mucin on the surface of the mucosa, thus reinforcing this protective insulating layer, in a form which is not readily removed by a flow of gastric juice from the glands. In addition, the buffering and neutralizing actions of the aluminum hydroxide would be improved by the increased secretion of mucus and the buffer action of the aluminum hydroxide would counteract the parietal cell stimulation by low concentration of SDS.

CONCLUSIONS

Using a simple method, developed in our laboratory, for producing ulcers in rats, we have evaluated a number of therapeutic agents used in the management of gastric and duodenal ulcer for their ability to protect the rumen against ulcerations and for their antacid and antipeptic action. Included in the study were Sodium Dodecyl Sulfate and colloidal aluminum hydroxide, singly and in mixtures, magnesium aluminum silicate, magnesium oxide, di-basic aluminum aminoacetate, magnesium trisilicate, and sodium bicarbonate. The protection of the rumen mucosa was greatest but not complete with Sodium Dodecyl Sulfate and colloidal aluminum hydroxide used singly. The other agents showed a diminishing protective action in the order in which they have been enumerated above. Sodium bicarbonate was the least effective. When combined in a mixture, Sodium Dodecyl Sulfate and colloidal aluminum hydroxide exhibited synergistic beneficial effects and protected the rumen against ulcerations completely. The practical possibilities of combining these two agents in the treatment of gastric and duodenal ulcer are discussed. Our results accent the importance of pepsin in the development of ulceration. With a pH which is just low enough to allow pepsin to act, severity of ulceration was found to be directly related to the "peptic activity" of the recovered gastric contents and was not dependent upon further variations in acidity or in "pepsin concentration."

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The Value of Gastroscopy as a Diagnostic Aid in Gastric Lesions*

By

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DESPITE THE strides in gastroscopy that took place since the invention of the flexible gastroscope in 1932, and not withstanding the great service that this diagnostic procedure can and does render in many perplexing clinical problems, this method of examination has not as yet become common knowledge or practice. It is in the hope that a larger body of practitioners will make use of gastroscopy, that this paper is presented.

Gastroscopy should be used by the gastroenterologist and internist just as cystoscopy is employed by the urologist.

The indications and contra-indications for gastroscopy were definitely established by such well-known gastroscopists as Schindler (1), Ortmayer (2) and Barnett (3).

It should be mentioned that the most important real contra-indications, obstruction of the esophagus or of the cardia, should not be excluded by the X-rays alone because sometimes they fail to show the obstruction. The thick Ewald tube should therefore be routinely introduced.

DANGERS

In 1940 Schindler (4) reported the results of a questionnaire concerning fatalities in relation to gastroscopic examinations. In all, 22,351 gastroscopic examinations were reported. In this series there were eight perforations of the stomach and one of the jejunum, but none of these terminated fatally. One patient died nine days after the examination, but whether the latter was directly responsible for the fatal outcome could not be definitely established. Another fatal case was reported by Paul and Lage (5) which was the 539th

gastroscopic examination performed at the University of Iowa. Others have recorded complications, none of which were fatal (6). Thus the fatality of gastroscopy is practically negligible.

The following ten cases were selected from more than two hundred patients that I gastroscoped at the Cumberland and Brooklyn Jewish Hospitals.

Everyone of the cases reported below was a problem clinically, roentgenologically and gastroscopically. I hope that they will serve to further illustrate the uses and limitations of gastroscopy as a diagnostic aid.

As there have been voluminous reports by gastroscopists on the diagnosis of gastritis by gastroscopy, I found it superfluous to include cases of this kind.

Case 1. A. P., age 48, female, white, housewife, was admitted to the Cumberland Hospital on December 29, 1939, complaining of intermittent epigastric pains for four years. Prior to admission to the hospital, her pains had increased in severity and frequency, coming on every four hours and awakening her at night. They were aggravated by solid foods and relieved by milk or cream. Her appetite was poor and there was a tendency to constipation. There was no evidence of bleeding into the stomach or bowel.

Abdominal examination revealed tenderness in the right upper and both lower quadrants.

The provisional diagnosis was peptic ulcer.

X-ray studies of the gastro-intestinal tract on February 2, 1940, were indicative of a duodenal ulcer. The patient was discharged on February 8, 1940, condition improved.

She was readmitted to the hospital on May 5, 1940, complaining of abdominal pains which were relieved by vomiting for 24 hours preceding her admission.

Abdominal examination revealed tenderness in the epigastrium. The clinical impression was the same as on the previous admission.

Fluoroscopic and radiographic studies of the gastro-intestinal tract on May 22, 1940, resulted in the diagnosis of periduodenitis or periduodenal adhesions with a possible gastric ulcer.

Gastroscopic examination on June 5, 1940, revealed a deep erosion, 1½ cm. in diameter with a grayish-green

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floor, situated in the pre-pyloric region, just above the angulus on the lesser curvature and near the anterior wall of the stomach. The edges were sharply outlined and slightly elevated. The surrounding mucous membrane was congested and edematous. The rest of the stomach showed evidence of hypertrophic gastritis. This was interpreted as a penetrating, benign, gastric ulcer.

The patient was treated medically and gastroscopied again on June 19, 1940. The ulcer described on the previous examination was definitely smaller and showed signs of healing. The patient at this time was symptom free.

Radiographic study of the gastro-intestinal tract on June 26, 1940, revealed a permanent deformity of the duodenal bulb indicative of duodenal ulcer. No mention of a gastric ulcer was made.

A third gastroscopic examination done on July 3, 1940, showed the ulcer on the lesser curvature, practically healed; only a scar remained.

Analysis of the gastric contents revealed fasting free—HCL—50 units, total HCL—65 units. After histamine, free HCL—100 units, total HCL—120 units. Other laboratory findings were negative.

The patient was discharged on July 1, 1940, apparently well.

A roentgenographic study of the gastro-intestinal tract made on January 1, 1941, resulted in the diagnosis of a healed duodenal ulcer. There was no evidence of a gastric ulcer.

The patient was readmitted to the surgical service of the Cumberland Hospital on November 30, 1941, for a gynecological condition and on December 2, 1941, a supracervical hysterectomy was performed.

Following the operation, the patient coughed and vomited a great deal after meals, which resulted in a wound evisceration and shock on December 9, 1941. She died on December 10, 1941, and came to post-mortem examination on December 11, 1941.

Post-mortem findings:

The stomach showed numerous prominent rugae. A calloused ulcer on the lesser curvature at the incisura angularis, measuring 2 by 1 cm. in diameter, was noted. No ulcer of the duodenum was found.

Comment:

In this case, the gastroscopic examination, not the X-ray, revealed the existence of a gastric ulcer. Furthermore, the gastroscope was of value in following the progress and course of this lesion.

Case 2. S. I., age 60, Norwegian, was first seen in the gastro-intestinal clinic of the Cumberland Hospital on September 13, 1941. He complained of dull, epigastric pains for the past year. They began with the intake of food and lasted fifteen to twenty minutes. The pains were confined to the epigastrium, did not increase in intensity, nor did they occur during the night. There was no history of nausea, vomiting or pyrosis. The bowels were markedly constipated but no blood was noticed in the stools. The patient's appetite failed for the past year and he lost 12 lbs. in the past six months.

Abdominal examination revealed a resistance in the right upper quadrant and epigastrium which suggested an underlying mass.

The primary diagnostic requirement was the exclusion of a gastric carcinoma.

The gastric contents were examined and showed free HCL—20 units, total HCL—30 units.

Fluoroscopic and radiographic studies of the stomach and intestines on October 2, 1941, were interpreted as possible early carcinomatous infiltration. Another X-ray series taken on October 27, 1941, revealed no evidence of peptic ulcer or new growth in the stomach or duodenum.

Gastroscopic examination on December 6, 1941, showed

an infiltration of the mucous membrane over the greater curvature extending from the antrum to the mid-portion of the stomach. The impression was: Malignant infiltration (carcinoma) of the greater curvature of the stomach.

The patient was admitted to Mount Sinai Hospital, New York, on December 14, 1941. After abdominal examination, a mass to the left of the median line was suspected.

Roentgenographic study of the stomach and intestines showed a filling defect along the greater curvature which was interpreted as carcinoma.

Exploratory laparotomy was done and enormous, giant rugae were found in the body of the stomach, which resembled a carcinoma. An incision was made into the stomach, the latter was explored, but no evidence of carcinoma was found.

The patient was discharged on January 24, 1942, in good condition. He was last seen in our clinic on January 6, 1943, feeling fine.

COMMENT

This is a case where all our diagnostic methods, including gastroscopy and X-ray, failed to establish a correct diagnosis. Exploratory laparotomy clarified this diagnostic problem.

Case 3. M. H., age 56, white, male, single, ship worker, was admitted to the Cumberland Hospital on April 9, 1942.

Three or four months before admission, he began to suffer from abdominal pains, progressively increasing anorexia, tarry stools, weakness, constipation, regurgitation of bitter material and a weight loss of 30 lbs. At the onset, the pains came immediately after the intake of food. On the admission to the hospital, the pains were continuous and extended from the left flank to the epigastrium. He rejected all foods, especially solids.

Physical examination:

The left upper quadrant of the abdomen was tender. No masses were visible or palpable. Rectal examination was negative.

The clinical opinion was carcinoma of the gastro-intestinal tract, probably in the stomach.

Radiographic examination of the gastro-intestinal tract on April 15, 1942, revealed a gross intrinsic defect on the lesser curvature of the stomach. The presumptive diagnosis was carcinoma.

Gastroscopic examination on April 18, 1942, revealed a grayish nodular infiltration of the mucous membrane on the lesser curvature, in the pre-pyloric region, reaching to the anterior wall and probably the greater curvature of the stomach. The infiltration involved the body of the stomach almost to the cardiac end. The reasonable inference was that we were dealing with a malignant infiltration of the inoperable type.

Analysis of the gastric contents before and after histamine revealed no free HCL. Examination of stools for occult blood on three occasions was positive.

Based on the X-ray findings, the patient was operated upon.

Postoperative diagnosis:

Inoperable carcinoma of the stomach with metastasis to the regional lymph nodes, liver and spleen.

COMMENT

In this case the X-ray and the gastroscopic findings were in agreement as to the nature of the lesion. However, the gastroscopic description was more detailed as to the extent of the pathology and therefore as to its inoperability. The surgical findings were consistent with the gastroscopic diagnosis.

Case 4. T. M., age 57, white, male, was admitted to the Cumberland Hospital on February 18, 1943.

Three weeks before admission, the patient began to suffer from constant epigastric pains associated with pyrosis. The pains were not related to food and not relieved by alkalies. He had lost 6 to 8 lbs. during the past few months. In the last few days, the patient had been coughing up small amounts of dark blood. He also noticed abnormally dark stools.

Physical examination revealed nothing abnormal.

This patient was referred to me for gastroscopy with a clinical diagnosis of malignancy of the stomach.

Fluoroscopic and radiographic examination of the gastro-intestinal tract on March 3, 1943, resulted in the following opinion: "There is a suggestion of a small malignant tumor in the pyloric region."

Gastroscopic examination made on March 6, 1943, disclosed no pathology.

The stool examination for occult blood on two occasions was negative. Gastric analysis—fasting specimen—free HCL—38 units, total HCL—40 units.

Another X-ray series was made on March 24, 1943, and now was interpreted as "a polypoid structure rather than a carcinoma."

The patient was operated on and no pathology in the stomach was found.

A specimen of the partly resected stomach was diagnosed histologically as gastritis.

COMMENT

This case was diagnosed clinically as gastric malignancy. Roentgenological examination on two occasions was inconclusive, in fact, erroneous. The gastroscopic examination revealed no gross pathology of the stomach and at operation no pathology of the stomach was found. This striking instance illustrates the inestimable value of gastroscopy as an aid in the diagnosis of gastric lesions.

Case 5. W. C., age 56, white, male, chauffeur, was admitted to the Cumberland Hospital on May 14, 1941.

The patient began to lose his appetite four months ago. For the past three weeks, he vomited occasionally after meals, which became more frequent at the time of admission. Twelve days ago, he began to suffer from a gnawing pain just above the umbilicus. It came on from one to one and a half hours after meals, was severe and was somewhat relieved by vomiting but not by food or alkalies. He had lost from 20 to 25 lbs. and complained of weakness. There was a history of dark stools, although on the day before admission the stool was not black.

Physical examination revealed no masses or tenderness when the abdomen was palpated. Rectal examination was negative. The provisional diagnosis was carcinoma of the stomach.

The radiologist's report dated May 28, 1941, was as follows: "A narrowing of the pyloric region due to the presence of an ulcerating neoplasm." Another series was made on June 4, 1941, and now a juxta-pyloric ulcer on the gastric side of the lesser curvature was diagnosed. The possibility of an associated malignancy was considered.

Gastric analysis—fasting specimen—free HCL—40 units, total HCL—50 units.

Gastroscopic examination on June 7, 1941:

The pyloric opening was seen contracting and relaxing normally. On the lesser curvature, in the pre-pyloric region, there was three superficial erosions, linear in shape, with exudate in their bases and radiating toward the pyloric opening. These lesions did not appear to be

malignant. The rest of the mucous membrane of the stomach showed evidence of advanced hypertrophic gastritis.

The patient was kept on an ulcer regimen and another gastroscopic examination was made on June 14, 1941. The superficial erosions originally seen through the gastroscope were not found at this examination (probably healed). The hypertrophic gastritis was considerably reduced.

In view of the clinical impression and X-ray findings, a laparotomy was performed. A small, hard, indurated area about $\frac{3}{4}$ cm. in diameter was found on the anterior wall in the pyloric end of the stomach and a similar palpable area on the posterior wall in the pyloric end of the stomach. The area on the anterior wall was grayish-white. This was suggestive of a benign pre-pyloric ulcer.

The pathological diagnosis was benign gastric ulcer.

COMMENT

The surgical as well as the pathological findings were consistent with the gastroscopic report. This is an interesting example where the gastroscope was the only instrumental method that revealed the true nature of the disease.

Case 6. J. T., female, age 52, Porto Rican, housewife, was admitted to the Cumberland Hospital on April 29, 1941, stating that for an indefinite period of time she had suffered from epigastric fullness and excessive belching after meals. In the last month she had suffered from anorexia and lost 20 lbs. Three weeks ago, she noticed black stools. For the past three days, she has had sharp epigastric pains and vomited mucus. On the day of admission, she vomited about "two glasses of bright red blood" and showed symptoms and signs of anemia. Alcoholism was admitted.

Findings on examination:

Tenderness was elicited in the epigastrium and in the left lower quadrant. Rectal examination was negative.

Clinical impressions:

1. Alcoholic gastritis.
2. Cirrhosis of the liver with oesophageal varices.
3. Bleeding peptic ulcer (probably arteriosclerotic).
4. Gastric malignancy.

Fluoroscopic examination of the gastro-intestinal tract on May 7, 1941, failed to show evidence of an ulcer of either the stomach or duodenum. Radiographic examination, however, revealed a penetrating ulcer on the lesser curvature, high up in the body of the stomach.

Another fluoroscopic and radiographic examination of the stomach and intestines done on May 14, 1941, was entirely negative.

Gastroscopic examination on May 17, 1941, revealed the mucous membrane in the body of the stomach to be hyperaemic. On the lesser curvature there was a small lesion, sharply outlined, about $\frac{1}{2}$ cm. in diameter with a greenish gray base. From the gastroscopic point of view, we were dealing with a definite benign ulcer.

Laboratory findings:

Analysis of the gastric contents revealed the fasting specimen—free HCL—0 units, total HCL—25 units. The specimen after histamine—free HCL—25 units, total HCL—40 units. The stool examination on May 8, 1941, was negative for occult blood.

COMMENT

In this case, the reports of the radiographic studies of the stomach and intestines on two separate occasions were contradictory. The gastroscopic examination clearly revealed a benign ulcer on the lesser curvature

in the body of the stomach. This was the only diagnostic procedure that reflected the true state of facts.

Case 7. E. M., age 58, male, single, white, undertaker, was admitted to the Cumberland Hospital on October 25, 1940. Two months ago the patient began to suffer from intermittent abdominal pains beginning around the umbilicus and radiating over the entire abdomen. This was accompanied by loss of weight and appetite. In the past three weeks, the pains became severe and constant, somewhat relieved by belching and flatus. The pains were worse at night and relieved moderately by the intake of milk. During this time, the patient vomited daily after meals. The vomitus was described as foul-smelling and contained some fragments which resembled "coffee grounds" but no gross blood. Milk and eggs were retained by the stomach. The patient also complained of moderate constipation and noticed black stools during the past week. Alcoholism was admitted.

Physical examination was practically negative.

The clinical impressions were:

1. Generalized arteriosclerosis.
2. Chronic alcoholism with alcoholic gastritis.
3. Possible carcinoma of the stomach.

Laboratory findings:

Gastric analysis of fasting specimen on November 1, 1940, free HCL—0 units, total HCL—5 units. The specimen after histamine—free HCL—35 units, total HCL—45 units. Blood was positive in all the specimens. Analysis of the gastric contents done on November 7, 1940, revealed no free HCL even after histamine was given.

Fluoroscopic and radiographic study of the gastro-intestinal tract done on October 30, 1940, was suggestive of carcinoma on the lesser curvature of the stomach in the pre-pyloric region with retention of a half of the barium meal on the 6 hour examination.

Gastroscopic examination on November 9, 1940, revealed a lesion in the pre-pyloric region on the lesser curvature, the size of a dime with a grayish green base. Its borders were at the same level as the rest of the mucous membrane, which was edematous and hyperaemic. The remainder of the stomach was normal. The gastroscopic impression was malignancy of the stomach in the operable zone.

The patient refused surgery. He was discharged from the hospital on November 12, 1940, condition improved. The patient continued to be symptom free while reporting to the clinic.

On February 8, 1941, the patient was gastroscoped again and the lesion described previously was seen, irregular in outline with a somewhat nodular base and grayish exudate.

A third gastroscopic examination October 11, 1941, revealed a lesion which was smaller than the one above described, the borders of which were sharply outlined. It was located in the pars media rather than in the pre-pyloric region. The question of an independent, old, benign ulcer had to be considered.

Radiographic studies of the gastro-intestinal tract on January 21, 1943, suggested malignant infiltration along the lesser curvature of the pre-pyloric region and evidence of an old, benign ulcer along the lesser curvature of the body of the stomach.

The patient was readmitted to the hospital on November 8, 1943. A month ago his gastro-intestinal symptoms became aggravated, resulting in loss of weight. He also complained of pains in the chest.

X-ray studies of the gastro-intestinal tract done on November 29, 1943, revealed the previously reported, penetrating ulcer in the pars media on the lesser curvature of the stomach still present. No mention was made

of the malignant infiltration of the pre-pyloric region. An X-ray of the chest taken on November 21, 1943, showed metastatic lesions in both lungs.

The patient became mentally disoriented and was transferred to a state institution.

The report of the Creedmoor State Hospital was as follows:

X-ray of the chest on December 23, 1943, showed two circumscribed areas of consolidation, one in each lung. The one in the right lung had an area of decreased density in its upper portion, suggesting a cavity.

Radiographic examination of the gastro-intestinal tract on January 7, 1944, showed no defect in the stomach or intestines.

The provisional diagnosis was cancer of the lungs with encapsulated pus. The patient died January 29, 1944.

An autopsy was performed and the important finding was primary carcinoma of the lungs proven microscopically. The gastro-intestinal tract showed no evidence of gross pathological findings.

COMMENT

This is a striking instance where clinical and radiographic studies, as well as gastroscopic examinations failed to throw light on what this man was suffering from.

Case 8. C. O., age 41, white, male, laborer, was admitted to the Cumberland Hospital on July 4, 1940, complaining of "burning pains" across the abdomen, just below the epigastrium, for the past 14 days. The pains were accompanied by nausea without vomiting. They occurred one hour after meals and were promptly relieved by food, milk or bicarbonate of soda. His stools were tarry until two days before admission to the hospital. The appetite was good. For many years, he had suffered intermittent attacks of dyspepsia and pain after meals.

On physical examination the patient was markedly pale. Palpation of the abdomen disclosed tenderness at a point midway between the xiphoid and umbilicus. There was voluntary rigidity to the left of the epigastrium. The provisional diagnosis was bleeding peptic ulcer with secondary anemia.

Fluoroscopic and radiographic examination of the gastro-intestinal tract on July 11, 1940, was negative. Examination of the stools for occult blood was positive. This became negative at a later date. Gastric analysis—fasting specimen—free HCL—0 units, total HCL—15 units. Specimen after histamine—free HCL—15 units, total HCL—25 units. Blood studies showed evidence of secondary anemia.

Gastroscopic examination on July 20, 1940, revealed the angulus and pyloric opening somewhat eccentric. The mucous membrane in the pre-pyloric region was atrophic with mucus adherent to it. On the lesser curvature, toward the posterior wall, there were two shallow erosions surrounded by hyperaemic mucous membrane. No bleeding was noticed over these erosions. The gastroscopic impression was atrophic gastritis with superficial mucosal erosions.

COMMENT

This case illustrates that the diagnosis of gastritis with superficial mucosal erosions as well as simple gastritis can be made only by gastroscopy.

Case 9. C. N., age 43, white, male shipfitter, was admitted to the Cumberland Hospital on November 7, 1944.

For the past three-years, the patient suffered from epigastric pains which radiated to the back and chest. The pains were more or less constant without any relation

to food and became progressively worse in the past few weeks. His appetite was poor and there was a weight loss of 20 lbs. The bowels moved daily with no evidence of bleeding. There was a history of vomiting occasionally after meals.

Physical examination revealed tenderness over the entire abdomen. The provisional diagnosis was gastric malignancy.

Laboratory findings:

Blood study showed evidence of secondary anemia. Analysis of the gastric contents revealed the fasting specimen—free HCL—0 units, total HCL—8 units. The specimen after histamine—free HCL—70 units, total 74 units. The stool examination was positive for occult blood.

Fluoroscopic and radiographic examination of the gastro-intestinal tract on November 14, 1944, revealed a penetrating ulcer on the lesser curvature in the pars media of the stomach. This was interpreted as a possible malignant ulcer. There was a 50% gastric residue on the 6 hour film.

Gastrosopic examination on November 18, 1944, disclosed a lesion on the lesser curvature in the body of the stomach, the size of a split pea, the borders sharply outlined and the base grayish in color. The mucosal folds were radiating toward the lesion. The gastrosopic impression was a penetrating, benign ulcer.

The patient was operated upon November 29, 1944. The findings were as follows:

A chronic, bleeding gastric ulcer along the lesser curvature of the stomach. This ulcer was penetrating and adherent to the pancreas.

The pathological report was chronic (peptic) ulcer of the stomach.

COMMENT

This case was diagnosed both clinically and roentgenologically as gastric malignancy. The gastrosopic impression of penetrating, benign ulcer of the stomach was consistent with the surgical findings and the pathological report.

Case 10. L. B., age 31, male, white, salesman, reported to my office on December 8, 1942, complaining of abdominal pains of three months duration. At first the patient interpreted these as hunger pains. Later on, the pains occurred daily; at 11 A. M., at 3 P. M., and awakened him at night. At times the pains were relieved by milk or food. His appetite was good. Pyrosis was present only when he had the pains. The bowels moved daily. There was no history of nausea or vomiting.

Physical examination revealed nothing abnormal except for tenderness in the epigastrium.

The clinical impression was peptic ulcer (duodenal) or possible gall-bladder pathology.

Prior to his visit to me, he had had a roentgenographic study of his gastro-intestinal tract which was reported as negative.

The stomach and duodenum were again X-rayed on January 15, 1943. The films showed a penetrating ulcer on the lesser curvature of the body of the stomach. The stool examination for occult blood, with the patient on a meat free diet for 72 hours, was positive.

Complete bed rest and ulcer regimen were instituted and on February 8, 1943, the stool was still positive for occult blood. Abdominal examination at that time revealed a tender mass in the epigastric region. As a result of these findings, the diagnosis of gastric malignancy was considered and the patient was admitted to the Brooklyn Jewish Hospital on February 15, 1943.

Gastrosopic examination on February 19, 1943, disclosed the following:

The angulus and pyloric opening were seen. The mucous membrane in that area was edematous, thickened and hyperaemic. In the antrum, extending to the body of the stomach, one could see a linear thickening, cord-like projection, nodular in appearance, with hemorrhagic areas in the same vicinity. The gastrosopic picture corresponded to one of the cases described by Schindler (7) and interpreted as lymphoblastoma of the stomach. A diagnosis of lymphoblastoma or lymphosarcoma was tentatively made.

A fluoroscopic and radiographic examination of the gastro-intestinal tract was made on February 18, 1943. The findings, reported at a later date, were suggestive of lymphosarcoma.

Laboratory findings:

Gastric analysis—free HCL—0 to 40 units, total HCL—18 to 65 units. All gastric specimens were positive for blood. Stools examined for occult blood on two occasions were positive. Red blood cell count and hemoglobin were indicative of secondary anemia.

The patient was operated upon on February 26, 1943, and a subtotal gastrectomy was done.

Pathological diagnosis: Resected stomach—lymphosarcoma.

The patient made an uneventful recovery and was discharged from the hospital March 20, 1943, for follow-up in the gastro-intestinal clinic. He was also referred for radiotherapy.

Radiographic study of the stomach and intestines on May 18, 1943, showed a gastrectomy with only the cardiac end of the stomach remaining. The barium poured readily through the ostium into the jejunum, the coils of which filled well. The progress of the meal at the six hours was normal.

The patient has been symptom free. His appetite has been good and he has been gaining weight.

COMMENT

The above reported case was extremely interesting from the clinical, roentgenological as well as from the gastrosopic point of view. The age, the rapid clinical developments, persistence of occult blood in the stools, the failure to respond to strict ulcer regimen, the rapid radiographic changes and the gastrosopic findings made the diagnosis of lymphosarcoma possible.

SUMMARY AND CONCLUSION

1. A reference to the indications, contra-indications and dangers of gastroscopy is presented.
2. Ten cases were selected from more than two hundred patients that were gastroscoped, some of them more than once.
3. Each of the cases reported, represented a clinical as well as roentgenological diagnostic problem.
4. All but two of the patients, No. 6 and 8, were either explored surgically or came to post-mortem examination.
5. In eight of the cases, the gastroscope proved to be of definite value in establishing the diagnosis. In two cases, the gastrosopic examinations failed in making the diagnosis and the clinical and radiographic examinations had likewise failed.
6. Many of the indications for gastroscopy are borne out by the cases reported.
7. It should be emphasized that gastroscopy is a valuable aid in diagnosing gastric lesions only in conjunction with a well taken history, physical examination, radiographic study and other laboratory data.

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Pruritus Ani: A Review of Oral Therapy

By

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IN THE original article on oral therapy for pruritus ani, (1), 42 cases were reported by the author and their progress described. Sodium dilantin, (diphenylhydantoin), employed originally in treatment of epilepsy, and taka-diasatase, gr. V; novatropin, gr. 1/24; phenobarbital, gr. 1/3 and sodium dilantin, gr. lss was given four times per day, (one before each meal and one before retiring). All cleansing of the skin with soap and water was stopped; only olive oil or vaseline were used. Olive oil was employed to remove old vaseline. Bed clothes and underwear were laundered specially with mild soaps. Supplemental management included avoidance of alcohol, mineral oil, condiments and fried food. Occasional saline enemas were advised. In the office a twenty-five per cent silver nitrate solution was applied to fissures.

This routine, which represented the result of several years study of the problem, was applied to forty-two cases, most of whom responded satisfactorily in a short time. Since then, more cases have been added. It is now possible to review this method of treatment, with a follow-up on the earlier cases and observations on more recent ones.

The form of therapy used in this series has differed from others, in that it is oral and directed at the most likely site of origin of the condition, the nervous system, employing drugs which are used in the treatment of epilepsy. It contrasts definitely with local anal and perianal approaches heretofore employed with little, if any success.

The follow-up on the earlier cases brought out interesting and useful information. It showed that the medication must be used in considerable strength to bring about definite changes; must be continued for a long time; and that patients have to be guided and frequently observed until a good result has been obtained. It also showed that recurrences were not as common as had been originally predicted. There were some recurrences, however, and a few failures.

Many cases responded in a surprisingly short time. In rare instances some even cleared up in a few days or weeks. Even the average case showed some symptomatic relief within a few weeks. No particular change was noted in the skin at this time. Then came

a period of another few weeks, during which the patient made more gradual and steady progress. A definite change in color of the affected skin then took place. The redness gave way to a bluish tinge and this gradually faded until the eighth week, when it appeared normal in color. The skin fissures became shallow and disappeared as did the adjacent ridges, and sleeping was no longer a problem. Shortly after this the patient would report "no itch at any time."

Difficulties met with were many. It was not found possible to merely give the sufferer a capsule and thereby relieve him or her of the pruritus ani. It required the most careful supervision of details and constant encouragement to a few who would have given up treatment long before results were obtained. These people were all of a nervous type and some were difficult to manage. As soon as some relief was noted, however, they became most cooperative.

The first difficulty was in the management of the drugs. Taka-diasatase, aiding starch digestion which is often deranged in nervous indigestion, was found to be essential. A high B coli count in the stool, a consistent finding, suggested inability to digest carbohydrates. When this ferment was omitted, in three cases, and only dilantin sodium administered, no results were obtained. All three reported partial relief as soon as the taka-diasatase was added and they then continued onward to recovery. Novatropin seemed useful as an antispasmodic, though not essential. Phenobarbital was not required in all cases. It was helpful as a mild sedative and has usually been combined with dilantin in treatment of epilepsy.

Sodium dilantin (diphenylhydantoin) is the most important element in the formula. It is also the factor that has to be regulated most carefully as regards results and toxicity. The total daily dose employed here, and in epilepsy, is six grains. This is reduced if too much sedative effect is noted, a rather rare occurrence; it is a mistake to reduce it too promptly. Other toxic manifestations are dizziness, muscular incoordination, gastric disturbances, swelling and bleeding of the gums, excessive activity, or loss of weight. A rash appeared in three cases, although phenobarbital had not been included in the prescription.

Muscular incoordination appeared in one of the

earlier cases and in three of the latter group. Gastric distress was noted a few times and bleeding gums once.

Whenever possible large doses of dilantin are used; small doses producing no effect at all. Toxic symptoms were often transient and did not represent a great problem.

With five cases, sodium dilantin could not be used, either because of toxicity or its failure to help the condition. This was discouraging at the time but proved to be a most fortunate occurrence. It was true that the list of sedatives and anticonvulsants had been thoroughly combed and no substitute for sodium dilantin could be found. All other sedatives when pushed too far made the patient lethargic, whereas dilantin was useful because of its slight hypnotic effect. When confronted with this problem it was decided that therapy must still follow along the same basic lines. In epilepsy, a ketogenic diet is often employed with good results but in this rectal condition a high fat diet was out of the question. Further investigation uncovered the fact that glutamic acid, one of the amino acids, is occasionally used in treatment of petit mal. It is reputed to have been of value in decreasing the number of seizures in some instances. Therefore glutamic acid was used in place of sodium dilantin in five cases.

The first patient on whom it was employed showed an interesting response. A young man, thirty-six years old, exhibited the worst clinical picture among males of the entire series. His history of pruritus ani dated back four years. He had received X-ray treatments, countless local injections and had a bureau drawer full of ointments. When seen by me the condition had reached the most severe stage, with fissures, redness and ulceration spread out over a twenty-four inch circle centering on the anal canal. The scrotum was red, raw, weeping and exquisitely tender. The under side of the penis was similarly affected. The patient was almost out of his mind and was exhausted from sleeplessness.

He was given the original medication and routine instructions. He promptly became even more distressed. A fine barbitol type of rash covered his entire body; he said he had used phenobarbital many times before this without unpleasant effects. He was therefore given only taka-diastase gr. V and glutamic acid, in $7\frac{1}{2}$ grain tablets, four after each meal. Within one week a striking change took place. He estimated that barely twenty-five per cent of the itch remained. The weeping of the surfaces had indeed stopped, and the inflamed areas were dull and changing to a bluish tinge. In another week the area had greatly improved and it appeared normal at the end of five weeks. The itch had entirely gone by then. The barbitol rash slowly disappeared and seemed unaffected by the therapy. Others in this group recovered but more slowly and less spectacularly.

It was felt that glutamic acid might be useful when added to the original sodium dilantin formula. This was done in several instances with good results. One case, however, became much worse when the amino

acid was added, with itching more severe than when first treated. Withdrawal of this item permitted the case to go on-to recovery. This reaction is totally unexplainable at present. It shows again that careful regulation is required in each instance.

The most interesting information obtained from the discovery of this alternate form of therapy was that two drugs, dissimilar in type, could produce the same result in selected cases. Sodium dilantin is of considerable value in the treatment of grand mal epilepsy and glutamic acid has been employed mainly in cases of petit mal. Each is not particularly effective in the other field. Oddly enough this seems also to be true in different patients with pruritus ani. Just why this is so, is puzzling. It does fix, however, more firmly the rationale of this oral therapy in this difficult and chronic rectal condition. It is also interesting to note that some of these cases, treated only with taka-diastase and glutamic acid, cleared up without the use of any sedative medication.

Recurrences are to be watched for and a certain number expected because of the very nature of the condition as we now understand it. Factors which caused the original injury to the nervous system may still be operating. The patient may not have the strength or courage to combat conditions which can again "get them down." There is also the possibility that the nervous system will react the same way again and again, as it does with those who are "epileptic."

It was a pleasant surprise to find that recurrences were not too numerous and that they were rather easily controlled as soon as they appeared. Patients were ordinarily advised to decrease medication and gradually stop it, one month after all symptoms had been relieved. They were also told to take their capsules again promptly at the first sign of any recurrence. It was found that the patient could withstand severe nervous shocks without return of itching, if the perianal skin had been normal for a long enough time.

Cases which did not respond to treatment were as follows:—a young man with financial and marital troubles who took his medication irregularly; and older man with prostatic trouble who died of that condition some months later; a man with gastric ulcers who could not continue medication because of the severe abdominal distress it caused; a young man working under pressure sixteen hours a day; and one man and one woman addicted to alcohol. In two instances, about to be listed as failures tridione was substituted for other anticonvulsants. Prompt relief was noted and further study of this drug will be made. This makes a total of six cases out of one hundred and sixteen that failed to respond. There were also five cases who discontinued treatment, with unknown results.

In the literature on epilepsy, pruritus ani is not mentioned as an associated condition. Nor, in this series of cases has epilepsy been recorded. There have been a number of patients, however, who gave histories of "nervous breakdown", and it is possible that a neurologist could have unearthed more detailed information along these lines. Epilepsy is at best a vague

Patient	Sex	Duration	Recovery In	Recurrences	Cause of Recurrence
1. R. A.	F.	10 yrs.	12 wks.	none	
2. M. B.	M.	4 yrs.	5 wks.	none	
3. J. B.	F.	2 mos.	3 wks.	none	
4. M. B.	F.	1 yr.	2 wks.	none	
5. A. B.	F.	16 mos.	8 wks.	none	
6. R. B.	M.	16 yrs.	under tr.		
7. M. C.	F.	4 yrs.	16 wks.	none	
8. W. C.	M.	7 yrs.	2 wks.	none	
9. R. C.	F.	20 yrs.	6 wks.	occasional; slight	
10. J. C.	M.	1 yr.	4 wks.		
11. C. D.	F.	8 yrs.	4 wks.	occasional; slight	
12. C. D.	F.	many yrs.	stopped tr.	none	
13. J. D.	F.	2 yrs.	1 wk.	none	
14. S. D.	F.	few yrs.	4 wks.	none	
15. J. D.	M.	4 yrs.	6 wks.	none	
16. A. D.	F.	7 yrs.	under tr.		
17. M. E.	F.	4 yrs.	12 wks.	once	nerve strain
18. M. E.	F.	4 yrs.	5 wks.	none	
19. D. E.	M.	1 yr.	under tr.		
20. B. F.	F.	10 yrs.	4 wks.	none	
21. F. F.	M.	2 yrs.	failure	recurrences	working sixteen hrs. per da.
22. E. F.	M.	2 yrs.	3 wks.	none	
23. A. F.	F.	7 yrs.	under tr.		
24. A. F.	F.	7 yrs.	2 wks.	none	
25. E. G.	F.	10 yrs.	3 wks.	none	
26. J. G.	M.	10 yrs.	8 wks.	none	
27. S. G.	M.	7 yrs.	6 wks.	none	
28. M. G.	M.	few yrs.	3 wks.	none	
29. S. G.	M.	15 yrs.	8-10 wks.	none	
30. G. G.	F.	5 yrs.	3 wks.	none	
31. G. G.	M.	15 yrs.	under tr.	?	is resident of another city
32. E.H.	F.	7 yrs.	4 wks.	once	"nervous upset"
33. F.H.	F.	many yrs.	2 wks.	none	
34. T. H.	M.	2 yrs.	8 wks.	none	
35. T. H.	M.	2 mos.	2 wks.	none	
36. J. H.	M.	few yrs.	3 wks.	none	
37. R. H.	M.	3 yrs.	under tr.		
38. E. H.	M.	20 yrs.	10 das.	none	
39. T. J.	F.	Many yrs.	4 wks.	none	
40. J. K.	F.	4 yrs.	3 wks.	none	
41. J. K.	M.	10 yrs.	2 wks.	once	nervousness due to accident in family
42. F. K.	F.	7 yrs.	stopped tr.	recurrences	"nervous upset"
43. H. K.	F.	4 yrs.	8 wks.	none	
44. F. K.	M.	10 yrs.	4 wks.	none	
45. J. K.	M.	5 yrs.	4-6 wks.	none	
46. A. K.	M.	many yrs.	partial recovery		diabetic
47. F. K.	F.	many yrs.	5 wks.	none	
48. F. K.	M.	1 yr.	6 wks.	none	
49. H. K.	F.	7 yrs.	3 wks.	none	
50. G. K.	M.	5 yrs.	3 wks.	none	
51. A. K.	F.	20-30 yrs.	stopped tr.	itch reduced	alcoholic
52. S. K.	F.	1½ yrs.	stopped tr.		
53. F. L.	F.	7 yrs.	20 wks.	none	
54. S. L.	M.	5 yrs.	4 wks.	none	
55. M. L.	F.	3 yrs.	failure	recurrences	alcohol
56. C. L.	M.	10 yrs.	1 wk.	none	
57. B. L.	F.	many yrs.	6 wks.	none	
58. F. L.	M.	5 yrs.	8 wks.	none	
59. V. L.	F.	several mos.	under tr.		
60. M. L.	F.	8-10 yrs.	3 wks.	none	
61. M. M.	F.	2 yrs.	4 wks.	none	
62. M. M.	F.	7 yrs.	8 wks.	none	
63. J. M.	M.	30 yrs.	failure	recurrences	alcoholic; discontinued tr.
64. R. M.	F.	4-5 yrs.	3 wks.	none	
65. T. M.	M.	10 yrs.	3 wks.	none	

Patient	Sex	Duration	Recovery In	Recurrence	Notes of Recurrence
66. D. M.	F.	1 yr.	4 wk.	none	
67. S. M.	F.	many yrs.	4 wk.	none	"dermatitis agens"
68. G. M.	F.	3 yrs.	4 wk.	none	
69. M. M.	F.	3 yrs.	4 wk.	none	
70. J. M.	F.	2 yrs.	under tr.		
71. I. M.	F.	1 yr.	under tr.		
72. J. M.	M.	2 yrs.	under tr.		
73. I. M.	M.	2 yrs.	4 wk.	none	
74. M. M.	F.	10 yrs.	under tr.		
75. I. N.	M.	1 yr.	4 wk.	none	
76. J. N.	M.	20 yrs.	marked but no permanent	partial under tr.	
77. C. O.	M.	3 yrs.	4 wk.	recurrences	recurrent exacerbations
78. M. O.	F.	6 mos.	4 wk.	none	
79. V. O.	M.	2 yrs.	4 wk.	none	
80. S. P.	M.	1½ yrs.	4 wk.	none	
81. J. P.	F.	1 yr.	10 wk.	none	
82. J. P.	M.	3 yrs.	4 wk.	none	
83. I. P.	M.	Many yrs.	10 wk.	none	recurrent exacerbations
84. P. R.	M.	Many yrs.	4 wk.	none	
85. M. R.	F.	3 yrs.	more recurrences		
86. I. R.	F.	2 yrs.	3 wk.	none	
87. M. R.	F.	2 yrs.	2 wk.	none	
88. D. R.	F.	1 yr.	4 wk.	none	
89. M. R.	F.	2 yrs.	12 wk.	2 recurrences	"paroxysmal"
90. A. R.	F.	3 yrs.	4 wk.	none	
91. J. R.	M.	3 yrs.	3 wk.	none	
92. R. R.	F.	4 yrs.	stopped tr.		
93. M. S.	F.	4 yrs.	stopped tr.		
94. D. S.	F.	5 yrs.	4 wk.	occasional, slight	recurrences possibly related
95. K. S.	M.	5 yrs.	5 wk.	none	
96. H. S.	M.	4 yrs.	10 wk.	none	
97. C. S.	F.	4 yrs.	3 wk.	none	
98. I. S.	F.	5 yrs.	3 wk.	none	
99. P. S.	M.	20 yrs.	3 wk.	none	
100. K. S.	M.	7 yrs.	stopped tr.		
101. I. S.	F.	3 yrs.	4 wk.	none	
102. M. S.	M.	4 yrs.	4 wk.	none	
103. V. S.	F.	7 yrs.	4 wk.	none	
104. S. S.	M.	1 yr.	improved but stopped tr.		
105. T. S.	M.	5 yrs.	under tr.		
106. P. T.	M.	20 yrs.	failure		carcinoma of prostate
107. I. T.	F.	1 yr.	partial 4 wk.	not followed up	
108. W. T.	F.	many yrs.	3 wk.	once	"alliteration"
109. J. T.	F.	5 yrs.	2 wk.	none	
110. L. V.	F.	1 yr.	3 wk.	none	
111. S. V.	F.	3 yrs.	1 wk.	none	
112. M. W.	F.	10 yrs.	3 wk.	none	
113. K. W.	F.	10 yrs.	3 wk.	none	
114. H. W.	M.	3 yrs.	3 wk.	none	
115. M. W.	M.	5 yrs.	failure	not relieved	gastric ulcer
116. K. W.	M.	5 yrs.	2 wk.	none	

but will have to serve until a better one is given us. It has been defined by Lennox (2) as "paroxysmal cerebral dysrhythmia", and he believes that it is due to a peculiar chemical or physico-chemical constitution of neuron cells which causes various cell clusters to discharge at a rate, and with a voltage, that is both abnormal and functionally devastating. He notes that an accumulation of ketone acids in the blood exerts a soothing influence on nerves, as do sedatives. It is remarkable that the therapy, if not the entity, of pruritus ani is now found to parallel closely that of grand mal, petit mal and psychomotor seizures. This opens

up a large new field for investigation.

Oral therapy has proven satisfactory in so many cases of pruritus ani that I believe it can be employed as a basic treatment for this disease.

SUMMARY

1. Oral therapy was used in 116 cases of pruritus ani.
2. A formula containing taka-diastase and diphenylhydantoin (sodium dilantin) was used in most cases. Neither drug was effective alone.
3. Glutamic acid, with or without hydrochloric acid,

- was substituted for diphenylhydantoin in 5 cases; used as supplementary medication in 24 instances. This suggested that sedation is not always essential.
4. Of 116 cases, there were 6 failures, for which possible explanations could be found; 5 discontinued medication; 12 are still under treatment.
 5. Treatment was aimed at the most likely cause of the condition, a nervous state affecting digestion.
 6. Response was prompt in many cases; successful in a large majority; often speeded by the use of Ep-som Salts twice weekly.

7. Recurrences were noted in 14 cases; they were again relieved in all but one.
8. A careful routine must be followed with attention to oral medication, diet, laundry and protection of the skin while changes are taking place; the need of constant observation cannot be emphasized enough.
9. The following chart shows the extent of treatment required in various cases.
10. Review of the literature of pruritus ani still fails to disclose mention of therapy of this type.

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Psychotherapeutic Methods in Gastroenterology

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IN THE FIELD of gastroenterology very many patients have some degree or form of neurosis, psychoneurosis or even psychosis in conjunction with functional or organic disorders. This has been reiterated by Alvarez (1) and others.

The digestive tract is particularly liable to functional disorders of emotional origin, evidenced by motor, secretory, or sensory changes. This is because of its intimate connection with the involuntary nervous system, which includes the intrinsic automatic plexus of Meisner and Auerbach, the sympathetic and parasympathetic systems, which differ from each other in physiology and drug reaction, and the hypothalamus, the real primitive brain, which consists of a group of interconnecting centers at the base of the brain. It is connected with the special senses and with the cortex

as well as with the internal involuntary organs. (2), (3), (4).

Most psychoneuroses have anxiety or fear as a chief characteristic, very often coupled with chronic resentment or anger or depression. Less frequent components are compulsions, obsessions, and phobias. Conversion and somatization reactions may cause most any symptom group. (5), (6), (7).

Psychoneuroses develop only in persons with constitutional hyper-irritable nervous systems (8) who are confronted by situations, usually social, economic or sexual with which they cannot cope.

While such nervous troubles are not new, their incidence in recent times has without doubt increased.

It has been stated that this is the golden age of psychiatry. It should also be stated that it is the golden age of the psychoneurotic. The development of both have been aided by the fears, anxiety depression and insecurity engendered by wars to prevent wars, and by

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modern political, economic and social uncertainties.

The diagnosis should be made by positive characteristics of abnormal behavior rather than by exclusion. This can usually be done during the process of routine history taking and examination. It must not be forgotten however that behavior disorders are not all of psychogenic origin. They may also be caused by organic or chemical or nutritional nervous system changes, such as seen in brain tumors, encephalitis, cerebral sclerosis, small strokes, (9) general toxæmias from infections or chemicals, nutritional changes present in anaemia, vitamin deficiencies, pellagra, low blood sugar or chlorides, or endocrine disorders as seen in thyroid disease and menopause. Neuroses may be of somatopsychic as well as psychosomatic origin.

TREATMENT

Psychiatry and psychotherapy are closely related to what has been known as the "art of medicine." It is an attempt to understand it better, to convert it into a science, and to measure it. This is the opinion of Palmer (10) with whom I agree. All physicians have always practiced psychiatry and psychotherapy in some form or other, good or bad. Not all doctors, however, are good psychotherapists, many would rather not give medical attention to these nervous, time consuming, often unhappy, often ugly, often unreasonable and often aggravating patients.

Psychotherapy seldom achieves miraculous cures even in the hands of experts, popular magazine articles notwithstanding. The patient must be cooperative and interested as well as intelligent enough to help themselves.

The following procedures outline the things which have been found to be of greatest value in helping the patient with psychogenic disturbances. The methods are based upon clinical experience together with a perusal of psychiatric literature (11) (12) (5) (6) (7). In the opinion of this internist they represent all that the psychiatrist has to offer. Individual psychotherapeutic ability however depends upon an understanding of the "art of medicine."

It has been found of value to follow each procedure much in the order given, and to discuss each with the patient as far as individually advisable.

I. A FRIENDLY ATTITUDE. This the psychiatrist chooses to call "The Psychiatric Approach." The patient is very often restless, nervous, confused and often critical, irritable or ugly. He should be made to feel that the doctor is his friend and is interested in helping him to recover, rather than that the doctor is too busy to listen to his story. The patient must not be given the "brush off" with a slap on the back and the statement that there is nothing wrong and told to forget his troubles.

II. REASSURANCE. The best measure and a necessary preliminary for reassurance is a painstaking history and physical examination together with laboratory work, special tests and X-ray examinations. These should be repeated if necessary often enough to reassure the doubting patient, and also often enough to

convince the doctor that nothing has been overlooked, or has developed since previously examined. The anxious skeptical patients can often be reassured regarding their insides only by repeated examinations. They often go from one physician to another. I disagree with the statement by psychiatrists that only one examination should be done else the patient gets his attention fixed on certain somatic complaints. The patient should be told unequivocally of the negative findings and perhaps shown the laboratory reports or films in order to be most convincing.

During the process of routine history taking and examination a doctor has an excellent opportunity to appraise the patient's emotional status without the patient being aware of such a psychiatric examination. It must not be forgotten that many patients are likewise appraising the doctor.

III. GENERAL MEDICAL TREATMENT. Any deviation from normal should be treated. A balanced diet, adequate hours in bed, proper rest and exercise, control of excessive tobacco, coffee and alcohol. Also medical treatment of such things as thyroid or menopausal disturbances, anaemia, vitamin deficiencies, infections, etc. Such medical treatment often restores the patient to such a state of well being that self-confidence is restored.

Avoid non-essential surgery. At times, however, sinus disease, nasal obstruction, tonsils, bad teeth, hemorrhoids, varicose veins, pelvic lacerations, etc. should be corrected. Inferiority complexes may also be caused by poor hearing, bad eyesight, unsightly teeth, a disfigured nose, moles on face, or other defects.

IV. REEDUCATION. This is stressed in modern psychotherapy. When the physician is convinced that the symptoms are all, or in part, due to psychogenic origin, the following explanation to the patient regarding their mechanism has served a useful purpose:

1. The nervous system in the process of evolution has been developed for the purpose of transmitting stimuli from one place to another, and to remember experiences. It is arranged in nerve bundles throughout the body, and has a central switchboard, the hypothalamus or primitive brain, situated at the base of the brain. There is also much nerve tissue in the brain which has the function of storing and remembering facts and experiences and of thinking. The hypothalamus is connected with the brain cortex, and also with the special sense organs of sight, hearing, smell and taste, as well as with the internal organs, glands, skin and muscles. It serves to coordinate the workings of the internal organs, with the emotions and special senses. (13).

2. There are **INHERITED UNLEARNED NERVOUS BEHAVIOR ACTIVITIES** such as the **REFLEXES, INSTINCTS**, and normal **EMOTIONS** which are common to all families and species, the same as there are **INHERITED PHYSICAL CHARACTERISTICS**. Both are subject to individual variation, such as, for example, the nervous race horse compared with the lazy work horse. There are even families of race horses which run well only on a dry track (pro-

geny of Seabiscuit and of Man of War) while other families run well on a muddy track (progeny of Whirlaway and of Gallant Fox).

Inherited characteristics are said to be **CONDITIONED** when they have been influenced by past experiences. **EDUCATION** is a modification of unlearned activities based upon memory and past experiences.

3. **EMOTIONS** are the organic expressions of the **INSTINCTS**. When they are of short duration they are called fear, anger, joy; when of longer duration they are called **MOODS** or **TEMPERAMENTS**, characterized by anxiety, worry, depression, ugliness or unhappiness.

Different persons may react differently to the same circumstances or environment, due to both their inherited variations and to their various past experiences. For instance in case of a large group of people attending a certain movie or play, some of the group may weep, some may laugh, while some may remain unmoved. (14)

4. Every psychic tendency seeks an adequate bodily expression: such as fear — run, anger — fight, grief — weep, joy — laugh, desire for wealth or fame — ambition, desire for children (perpetuation of species instinct) — sex and marriage.

5. If this external expression of a psychic desire is blocked for any reason, such as law, public opinion, religion or moral belief, or social taboo, the impulse or stimulus may be short-circuited or switched, in the hypothalamus, over into the wrong nerve tract and hence the emotion finds its expression in the wrong part of the body. A simple example would be that of a person who has fear of an examination or speech, or other ordeal, in which the desire to run away, gets switched from the legs to the stomach, bowel or bladder, and is manifested in that organ. A more continuous fear, anxiety, anger or disappointment may cause a more chronic stimulation of various parts of the involuntary nervous system and be expressed as functional disorders of the digestive tract, such as hyperacidity, gastric spasm, possibly ulcers, biliary dyskinesia, constipation or diarrhea.

6. The adversities in a patient's life which have or are causing trouble may not always be revealed or may be purposely concealed in the patient's history. Frequently when a patient has been convinced as to the cause and nervous mechanism of his symptoms, he himself will recall earlier life episodes or troubles which have persisted in the subconscious mind, or he may reveal present worries or disappointments previously purposely undisclosed. Thus he may see the foolishness of his present symptoms.

7. The patient should learn to ignore minor symptoms and they will disappear.

V. **SUBLIMATION**. Psychic tendencies which would otherwise run wild and be harmful, are said to be sublimated when such energy is put to some harmless, useful, entertaining, social or educational use.

Most psychoneurotic people are selfish and self-

centered, they are thinking mostly of themselves and of their own present and future well being. They are filled with anxiety or disappointment. Sublimation is a means of helping them to get their minds off themselves.

This method of mental prophylaxis and therapy is most important and its possibilities for good should be given much study by every physician. It includes the study of subjects advisable in the art of living, as well as being helpful in smoothing troublesome mental adjustments. A study of these possibilities should be of value and a pleasure to the physician himself, as well as a help to his patients. Sublimation includes the study of such subjects as book-collecting, stamp-collecting, sea-shell collecting, scrap books of various subjects, literature, history, travel, astronomy, geology, botany, biology, photography, painting, music, cooking, house-keeping, sewing, dress designing, millinery, landscaping, gardening, farming, group activities in club, lodge or church, religion, painting, music, or sports, such as golf, bowling, fishing or hunting.

The individual patient should consider all possibilities and then take up one or two of them with determination to put all surplus time and energy into a thorough study of the subject.

It is often very difficult to get these self-centered worried people interested in anything else than themselves or their insides. This again is the art of medicine.

VI. **ENVIRONMENTAL CHANGE**. Man can usually adjust his environment, surroundings, or situation to fit his desires or abilities. At times, however, he is unable to do this, or to make a decision as to changes, it is then that a **COMPLEX** arises. In such situations the physician can often be of service with advice regarding environmental changes in connection with type of work, climate, location, marital troubles, marriage or divorce, use of contraceptives, or living within income.

VII. **RELAXATION**. Most patients with gastrointestinal psychosomatic reactions are nervous, tense and anxious. Alvarez has noted that these patients have hyperactive deep reflexes. (15).

Such patients need to learn how to relax. The following suggestions to the patient, typed and with instructions to read daily and memorize, has been found useful.

RELAX

1. Do not take life too seriously.
Do not be an idealist.
Things will not matter much 100 years from now (16).
Let the other fellow worry. Don't give a damn.
It is bad to continuously strive, even in a good cause.
2. Do not try to win or be the best.
Resign unnecessary obligations, work and commitments.
3. Learn to relax and rest at every opportunity.
You will do more work better if you do not hurry.

4. Avoid fatigue. Get 9 to 10 hours in bed every night.
5. Learn the value of masterly inactivity.
Avoid as far as possible, telephone, radio, newspapers and politics.
6. Avoid anger. Getting mad causes more bad effect on you than on the other fellow.
Avoid arguments. Do not interfere with others.
7. Cultivate a cheerful optimistic disposition.
Develop a sense of humor.
Remember, and repeat to others, humorous short stories which you have read or heard.
Read humorous short stories.
8. Avoid thinking constantly of yourself.
Ignore minor symptoms and they will be better.
9. Develop a hobby which will be useful, instructive and interesting.
It will take your mind off yourself.

VIII. Confession. Patients should be allowed, encouraged and urged to talk out their troubles. It is a form of mental catharsis which often gives relief. Their physician may be the only person in whom they have confidence enough to reveal their intimate troubles, and seek advice (19). A physician must, however, conserve his time and not allow loquacious frustrated patients to wander on at great length about irrelevant things.

IX. SUGGESTION. This form of psychotherapy is of good temporary value while observing the medical and emotional difficulties of the patient. It should not, however, be carried beyond a certain limit, into the realm of clairvoyance.

X. PSYCHOANALYSIS. This procedure will never become of great practical value because of the following reasons: 1. The patients must be young and physically healthy. 2. They must be above average intelli-

gence. 3. They must have plenty of time and money as the necessary conference with the psychiatrist requires quite 1 or 2 hours, 2 or 3 times per week, for 1 or years. and 4. The results from such procedures are not very conclusive. Recently a method has been called narco-synthesis, in which narcotics are given at the point of depressing the cortex and the hypothalamus simultaneously without producing sleep. This procedure, as with other psychoanalytical procedures, is used. It apparently is of some value as an adjunct in decreasing the time necessary to cure certain organic sources of anxiety. (17).

XI. SHOCK THERAPY. Such type of therapy has been shown to be of considerable value in psychoneuroses characterized by marked degrees of symptoms, but is of no value in the other psychoneuroses. Without doubt many patients with such tendencies have been at least temporarily saved from their own impulses by shock therapy. The mechanics of such therapy action has not been settled. Electroshock has apparently replaced the use of metrazol as of insulin in this form of therapy. It should be used only by trained, experienced psychiatrists.

SUMMARY AND CONCLUSIONS

The internist should give more attention to the psychosomatic aspect of his specialty. He should have better knowledge and appreciation of the needs of recognition and treatment of these functional behavior disorders and should then excel in psych. therapeutic ability because of his superior knowledge of physiology, biochemistry and clinical medicine. A short outline of the procedures which have been found of value in psychotherapy is given as a working basis.

Psychiatric study and literature has been a confusion of metaphysical and highly theoretical hypotheses which has bewildered the psychiatrists themselves (18). This has retarded the use of good psychotherapy by other medical men.

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Book Reviews

Gastroenterology in General Practice. By Louis Pelner, M.D. Pp. 285, (7.50), Charles C. Thomas, Springfield, Illinois, 1946.

While this book is adequate in its coverage, it is possibly too tabular to constitute a flowing style. There are few statements whose validity can be challenged. Above all, the text is perfectly adapted to quick reference by the busy general practitioner and it is pre-

eminently practical, in that the various forms of treatment are stressed. Where diets are advisable, these are always placed plainly in the text. The color plates (20 in number) are beautiful and instructive and the entire book is profusely illustrated. X-ray, gastroscopic and laboratory techniques are described. As an example of the publisher's art, it is a collector's piece. The book can be recommended especially to medical students.

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CLINICAL MEDICINE

STOMACH

CONTE, A. N. AND McNALLY, J. T.: *Congenital hypertrophic pyloric stenosis.* (*Arch. Pediat.*, V. 63, p. 1, 1946.)

A total of 30 cases (27 boys, 3 girls) are reviewed. Constipation was present in 29 of the children and 27 had vomiting of the projectile type. No tumor was palpable in 19 cases, but was palpated in 8 cases; 3 cases were doubtful. Operation (Rammstedt method) improved 14 cases and 10 recovered. Too early feeding after operation or too rapid increase in the concentration of milk mixtures after operation resulted in vomiting. — G. Klenner.

BOWEL

COOKE, W. T., ELKES, J. J., FRAZER, A. C., PARKES, J., PEENEY, A. L., SEMMONS, H. G. & THOMAS, G. (*Anomalies of intestinal absorption of fat.* (*Quart. J. Med.*, V. 15, p. 141, 1946.

The study reported here covers fat determinations in stools of 120 patients and the question of fat balance in relation to fat digestion and absorption. In normal individuals more than 95 per cent of the 50 gram fat test meal is absorbed, while in idiopathic steatorrhea the average absorption was 73 per cent of the test meal.

Included among the patients were 29 cases of idiopathic steatorrhea, 21 of sprue steatorrhea, 7 of pancreatitis, 2 of lacteal obstruction, and 20 cases due to malnutrition, surgery, or other known factors. Control cases were patients having diarrhea without steatorrhea

and included 15 cases, 12 cases with anemia, and 14 cases with gastrointestinal conditions.

Microscopic stool examination was found to be very unreliable for determining abnormal fat absorption even though sometimes fatty acid crystals in excess were seen. Gross stool appearance was not reliable since stools containing much fat did not always appear bulky and pale but frequently appeared normal in color and consistency. Neither determination of per cent fat in dried feces nor hydrolysis of fat for determination of unchanged fats are reliable. The authors think that correlating the fatty acids in dietary and fecal fat is a good means of determining fat absorption. Differential analysis of fecal fat holds no advantage over the simpler procedure of using marked meals given between saline enemas 2, 3 or 4 days apart. — M. H. F. Friedman.

FRIEDMAN, S. M.: *Position and mobility of the duodenum in the living subject.* (*Am. J. Anat.*, v. 79, p. 147, Jan. 1946.

The position of the duodenum was studied in approximately 450 hospital patients by means of serial roentgenograms. The highest point of the first portion of the duodenum lies between T12 and L3, with a mean position opposite the lower part of L2. The range is due in part to migration of the position point with age, at a rate approximately equal to one-half vertebra per ten years. The duodeno-jejunal flexure was found the most fixed point, at L1 to L3, and does not shift position point with age. Postural changes result in movements of the duodenum of about 2 vertebrae lengths, depending on the size and fullness of the stomach. The

duodenal downward excursions seems to pivot around a fixed point, the duodeno-jejunal flexure, resulting in shortening of the duodenal column. — M. H. F. Friedman.

Mosrs, W. R.: *Appendicitis: clinicopathologic study.* (*South Med. J.* v. 39, p. 902, Nov. 1946.)

Obstruction of the lumen of the appendix is responsible for the clinical picture seen in cases of "appendicitis." Venous obstruction, edema, and exudation of sero-sanguinous fluid develop to give the appendix the appearance seen at operation of acute stages. The appendix becomes permeable and even in the absence of any apparent perforations may permit passage of bacteria, thus resulting in localized peritonitis. Unless surgical intervention takes place, the appendix, because of the venous occlusion, proceeds to the stage of perforation due to devitalization through arterial occlusion, thrombosis, etc. Gangrene will be present but may not be extensive if the affected blood vessel is small. Bacteria are not responsible for the actual perforation; they only determine the presence of peritonitis, etc., and are to be regarded as secondary invaders. — N. M. Small.

DUNKERLEY, G. E.: *Perforation of ileum in enteric fever; notes on 22 consecutive cases.* (*Brit. Med. J.*, v. 2, p. 454, Sept. 28, 1946.)

During the decade of 1935-45 there were eleven perforations among 1077 cases of enteric fever treated in a southern Indian hospital. An additional eleven cases of perforation were found among the ambulant patients with enteric fever. In these 22 cases the most prevalent and constant symptom was sudden severe abdominal pain. In patients confined to bed perforation occurred about the tenth day while in ambulant patients it occurred within an average of 13 hours. Seven of the former and five of the latter died. Operation consisted of repair of the rupture with interrupted sutures and a continuous seromuscular suture, with omentum covering the perforated portion of bowel. — F. E. St. George.

RENSHAW, J. F., KISHADDON, R. M. AND TEMPLETON, F. E.: *Gastrocolic fistula — an experimental study.* (*J. Lab. Clin. Med.*, v. 31, p. 457, April, 1946.)

Patients with gastrocolic or gastroenterocolic fistula present symptoms consisting of vomiting, nausea, diarrhea. Cachexia and nutritional deficiency may also be shown. Shunting of the food out of the stomach directly into the colon, by-passing the small bowel, is the usual explanation for the syndrome. Reflux of the colonic contents into the stomach has also been suggested as the cause of the syndrome.

The authors studied the flow of a barium meal in nine patients and six dogs with gastrocolic, duodenocolic and gastroenterocolic fistulas. In four patients and in the experimental animals most of the meal passed down by way of the small intestine and not

directly into the colon. On the other hand, the barium was seen to enter the stomach directly from the colon. The authors suggest that the refluxing fecal current injures the intestinal and gastric mucosa so that the normal processes of absorption and secretion are impaired. — M. H. F. Friedman.

PANCREAS

ANDERSON, D. H.: *Pancreatic deficiency.* (*Am. J. Obstet. Gynecol.*, v. 70, p. 100, Aug. 1945.)

In infants with congenital pancreatic deficiency there is the possibility of immaturity of digestive organs other than the pancreas. This results in greater difficulty in therapeutic control. Lack of previous stores of essential food substances, limitations in diet, requirements for maintenance and growth pose special problems in nutrition. In general the caloric intake should be high, to allow for the inefficient utilization of the food. From 120 to 180 calories per kilogram are recommended. Fat should be low since it is not utilized well. Supplementary vitamins are given liberally.

Respiratory involvement almost always occurs. The prognosis is more favorable if the infant is affected after the sixth month rather than earlier. Penicillin has proved effective in treating the respiratory infection. — G. Klenner.

HARPER, R. A. K.: *Some observations on radiology of the pancreas.* (*Proceed. Royal Soc. Med.*, v. 39, p. 534, July, 1946.)

Examination of the stomach and duodenum is a valuable means of assessing the size of the pancreas and its relations to the surrounding viscera. Visualization of mucosal patterns, presence of erosions, and motility studies on the duodenum may yield important diagnostic information. Calcification of the pancreas and ducts are relatively easy to see. Smooth-filling defects of parts related to the pancreas may be due to cystic enlargement. The size and position of the cyst may be readily determined by the degree of displacement and the portion of the viscera displaced. Diagnosis of carcinoma of the pancreas may be made by noting the deformity produced and the presence of infiltration of the stomach and duodenum. Mere widening of the duodenal loop with a pressure effect is in itself not sufficient for diagnosis; the additional factor of erosion or invasion of the duodenal wall must be present. — F. E. St. George.

LIVER AND GALLBLADDER

WALTERS, W. AND HEIM, D. J.: *Structure of the common and hepatic ducts.* (*Proceed. Staff Meet. Mayo Clinic*, v. 21, p. 377, Oct. 2, 1946.)

The degree and extent of complications due to pathologic narrowing or obstruction of the bile duct system depend on the degree of stenosis and the nature of the pathology. Severe continued jaundice with rapidly developing liver damage results if the obstruction is not

relieved by surgery. Between 80 and 90 per cent of the duct strictures result from injuries in the course of operation on the gallbladder or ducts. Prevention of injury is possible only through adequate knowledge of inflammatory strictures; congenital defects are other factors responsible for occlusions of the common ducts. — D. A. Wocker.

MAIZELS, M.: *Empirical tests of liver function.* (*Lancet*, v. 2, p. 451, Sept. 28, 1946.)

Empirical tests of liver function utilizing excess gamma globulin are used to distinguish between jaundice of parenchymatous and obstructive origin, to assist in diagnosis of hepatitis without jaundice, and to follow the course of the disease and furnish prognosis. Four tests studied in order of their usefulness are: thymol turbidity test; cephalin-cholesterol flocculation test; colloidal scharlach red test; and the Takata Ara test, (Britton's modification).

The thymol turbidity test is the most simple and generally is positive in catarrhal jaundice, subacute and chronic hepatitis, and is negative in bile duct obstruction. This test is unlikely to be positive in carcinoma of the liver.

The cephalin-cholesterol flocculation test gives satisfactory results in the hands of some workers, but variations in reagents give conflicting data. This test is usually positive in catarrhal jaundice, subacute and chronic hepatitis.

The colloidal scharlach red test parallels the values given with the thymol turbidity test but is more likely to give positive results in infectious diseased and rheumatoid arthritis.

The Takata Ara tests give many false positives and are not of differential diagnostic value because they are often positive in both parenchymatous and obstructive jaundice. However, when this test is negative and associated with jaundice, it is probably obstructive in origin.

When duct obstructive jaundice gives positive empirical tests, serious complications such as infection and metastasis are commonly present; however, the latter may give negative empirical tests. Besides hepatitis, positive empirical tests can be given by myelomatosis, sarcoidosis, certain types of adenitis, rheumatoid arthritis, sulphonamide poisoning, and infestation by certain bacteria, protozoa, and viruses. — John L. Weaver.

ULCER

HODGSON, J. R., GOOD, C. A., AND HALL, B. E.: *The roentgenographic aspects of polycythemia vera.* (*Proceed. Staff Meet. Mayo Clinic*, v. 21, p. 152, Apr. 3, 1946.)

The roentgenograms of 88 cases of polycythemia vera were analyzed in an attempt to determine whether any changes in skeletal structure occurred which could be designated as characteristic of the disease. Incidental

to this study were roentgenologic observations on the gastrointestinal tract.

The gall bladder roentgenograms did not show any relation to the polycythemia. The incidence of peptic ulcer in these patients was found to be slightly less than 8 per cent as compared with the incidence of 2.5 to 3.0 per cent in the normal population. However, there is still insufficient evidence to establish a definite cause and effect relationship between polycythemia and duodenal ulcer. — D. A. Wocker.

SCHMASSMANN, HECTOR: *The medical treatment of ulcer ventriculi and ulcer duodeni with a preparation obtained from the gastrointestinal tract.* (*Schweiz. Med. Wochenschr.*, v. 74, p. 576, May 27, 1944.)

Fifty cases of gastric and duodenal ulcer were treated in the Cantonal Hospital of Winterhauer with a preparation from the mucosa of the hog's gastrointestinal tract. When treatment was effective the fresh ulcer niche disappeared in three weeks. In gastric ulcer patients, and in patients with gastritis, the hyperacidity was decreased but in patients with duodenal ulcer the acidity of the gastric secretion was increased. No demonstrable effect was noted in cases requiring surgical intervention. About half of the patients suffering relapses were improved again following another course of therapy. The extract was given parenterally. — M. H. F. Friedman.

EXPERIMENTAL MEDICINE

PHYSIOLOGY

PENNINGTON, HANEY, AND YOUNG: *Effect of distention of jejunum upon tonicity of the cardia of the dog.* (*Proc. Soc. Exper. Biol. Med.*, v. 62, p. 140, June, 1946.)

By using trained dogs with Thiry jejunal fistulas and esophageal fistulas, the effect of jejunal distention on the tonus and motility of the cardiac sphincter was studied. Recordings were made of the tonus shifts in the jejunum and in the cardiac sphincter by means of inflated balloons and a tambour recording arrangement.

The cardiac sphincter was relatively insensitive to jejunal pressure changes. If sharp distention of the jejunum was applied for a period of 1-3 seconds, relaxation of the cardiac sphincter was noted. Prolonged distention (10 seconds) or alternate rapid distention and relaxation failed to affect the results. The original state of tonus of the jejunal loop determined the amount of distention necessary to produce cardiac relaxation. The cardiac relaxation produced by jejunal distention was at least half of the maximal relaxation during deglutition. Normal tonus returned in 15-30 seconds. Jejunal distention was followed by no nausea or vomiting unless the internal pressure reached 60-80 mm Hg.

The authors conclude that while the cardiac region is relatively insensitive to distention of a short jejunal segment, cardiac relaxation without nausea may occur following distention. This is due to reflexes over unknown pathways. — J. Moffitt.

PATHOLOGY

HERBUT, P. A., WATSON, J. S., AND PERKINS, E.: *Hepatic and renal necrosis in alloxan diabetes of rabbits.* (*Arch. Pathol.*, v. 41, p. 516, May, 1946.)

A single intravenous injection of alloxan, 200 mg per kilo, was given to 30 rabbits. In 14 of the 25 animals (56 per cent) that died within 30 days, necrosis of the proximal convoluted tubular epithelium similar to that produced in bichloride poisoning was found. Uremia accompanied 8 of the 14 rabbits in the terminal stages. In 10 rabbits (out of 11) that died within the first four days there was found extensive necrosis of the peripheral portions of the liver lobules. In the pancreas the islets of Langerhans which become necrotic disappeared, probably as the result of proliferation of adjacent acinar cells rather than the result of mere resorption of the detritus of the collapsed "unsupported" islet cells. — G. Klenner.

PATHOLOGICAL CHEMISTRY

STOKES, G. D., GAMBILL, E. E., AND OSTERBERG, A. E.: *The methylene blue test for bilirubinuria: clinical and spectrophotometric observations.* (*Proceed. Staff Meet. Mayo Clinic*, v. 21, p. 267, July 1946.)

The nature of the methylene blue test for bilirubinuria was studied with the view of correlating the intensity of the reaction with the degree of hyperbilirubinemia. No perfect correlation was found when serum was used. When urine with artificially produced bilirubinuria was used the test became positive at a concentration of 2.0 mg. bilirubin per 100 cc. of urine. The color reaction is probably not due to some specific chemical reaction but to a blending of blue and yellow colors.

—H. Stilyung

MISCELLANEOUS

FRAPS, G. S.: *Digestibility of human foods and animal feeds as measured by digestion experiments with rats.* (*Bull. Texas Agric. Expt. Sta.*, v. 675, p. 1, 1945.)

The energy values of animal feeds and human foods were determined in 508 tests on rats and the results are compared with those previously obtained on chickens and with those reported on humans. The rats digested slightly less protein from the animal feeds and slightly more from the human foods than did the chickens, but less fat, more crude fiber and more nitrogen-free extract than chickens. Digestibility of protein and of nitrogen-free extract averaged practically the same for both rats and humans, but the digestibility of fats averaged a little lower in rats than in humans. Digestion experiments with rats appear to be a good measure of human digestibility.

—Courtesy of Biological Abstracts.

KROGER, W. S., AND DELEE, S. T.: *Psychosomatic treatment of hyperemesis gravidarum.* (*Am. J. Obstet. Gynecol.*, v. 51, p. 544, 1946.)

A series of nineteen women having intensive bouts of vomiting and nausea were subjected to hypnosis. The patients had not responded previously to other forms of therapy. The hypnosis was combined with either psychoanalysis or direct suggestion. Seventeen of the patients were completely relieved. The authors believe the method brings to the surface latent psychogenic factors responsible for the nausea and vomiting. The therapy acts by raising the vomiting threshold or by inhibiting the higher sensorium from visceral stimuli. The women developed nausea and vomiting as an unconscious expression of rejection of the pregnancy state or else believe that nausea and vomiting are necessary adjuncts to the pregnancy state. —I. M. Theone.

FRANK, E.: *Alloxan Diabetes.* *Türk Tıp Cemiyeti Mecmuası*, Vol. 12, No. 6, pp. 174-183, 1946.

Alloxan diabetes was produced in rabbits. Silver impregnation of the islets showed that the beta cells, in which insulin is produced, were entirely lacking. Injections of insulin corrected the hypoglycemia but not the microscopic picture. Author believes that alloxan may be produced in the human body and cause diabetes.

—O. Felsenfeld.

HRDLICKA, J. AND ROVENSKY, E.: *Adenomatous Polyp of the Duodenum.* *Lekarske Listy*, Vol. 1, No. 20, pp. 476-478, 1946.

A case report. The symptoms were those of a duodenal ulcer but X-ray examination permitted to establish the diagnosis. Operative treatment was followed by cure.

—O. Felsenfeld.

UHLIK, F.: *Cystadenomas of the Pancreas.* *Casopis Lekarů Ceskych*, Vol. 85, No. 33, pp. 1137-1141, 1946.

Pancreatic cysts are classified as: (1) parapancreatic cysts (hydatidous, lymphangiomatous or dermoidal), (2) cystic degeneration of the pancreas (Lindau's disease), (3) cystadenomas. The latter originate from remainders of Wolff's duct. A successfully operated case of cystadenoma is reported.

—O. Felsenfeld.

MUFIDE, KULEY: *Treatment of Ulcerative Colitis with Enemas Containing A Vitamin.* *Türk Tıp Cemiyeti Mecmuası*, Vol. 12, No. 8, pp. 266-269, 1946.

Author believes in the allergic background of colitis ulcerosa. A series of 20 to 30 daily enemas containing 250,000 to 300,000 units of vitamin A in tepid water or olive oil was very beneficial for the treatment of this disease. The enemas were retained for 10 minutes.

—O. Felsenfeld.

Nutritional Survey At a Children's Institution; Incidence of Avitaminotic Lesions and Effects of Therapy*

By

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A NUMBER OF nutritional surveys made in recent years of groups of children, both institutionalized and otherwise, have indicated an unexpectedly high incidence of lesions of nutritional deficiency among children in many communities, under a variety of conditions, and often regardless of economic status (1, 9).

In the investigation to be reported here, an unusual opportunity was afforded to study a series of institutionalized boys in a fairly wide age group (8 to 17). The majority came from various parts of New York State, the rest from scattered sections of the north-eastern portion of the United States. The institution itself is situated in open country on a large tract of land. Living quarters are in cottages, in each of which twenty boys reside with their supervisors. All the boys were sent to the institution because of behavior problems; the institution itself affords them the greatest possible physical freedom and a large share in their own self-government. At the time this survey was begun, there were approximately 425 boys in the institution. Of these 183 were included in the study; 167 were Caucasian, 16 were Negroes. The duration of residence of this group varied from three weeks to five years. Fifty-three came from the metropolitan area of New York City; 79 were from various other parts of New York State, 14 from Connecticut, 13 from Massachusetts, 8 from Ohio, 6 from New Jersey, 3 each from Pennsylvania and the District of Columbia, and one each from Maine, Illinois, Maryland and New Hampshire. About one-fourth came from self-sufficient middle class families; the remainder were less well favored economically.

Each of the boys in the group of 183 studied was examined for signs and symptoms of nutritional deficiency, with especial attention to deficiency of the water-soluble factors, during the spring and early summer of 1945. These children were then given nutritional therapy for periods up to seven months and were re-examined at one or more intervals during that time. The avitaminotic lesions were recorded routinely by color photography under standard conditions of exposure and lighting before and after therapy, and records of other data were made as indicated in Table I.

The findings are presented in detail in Table I (see page 129), and part of them in graphic form in Charts I and II.

The deficiency lesions were graded as slight, moderate and severe, indicated by one, two or three plus marks in Table I, and by the dotted bars in Charts I and II. The latter show proportions of the total (indicated by the height of the black bars) made up by the stigmas of varying severity.

Complete therapy in the form of a vitamin-mineral supplement and a fortified vitamin B complex syrup†† derived from liver extract and yeast autolysate, was administered routinely, with minor variations and omissions as indicated in Table I. This provided per day, on the average, the following nutritional factors: thiamine 10.5 mg.; riboflavin 11 mg.; pyridoxine 3.25 mg.; pantothenic acid 8 mg.; niacin amide 70 mg.; ascorbic acid 35 mg.; choline 4 mg.; vitamin A 4,500 units; vitamin D 640 units, and 8- tocopherol 2 mg., in addition to the extract derived from 18 Gm. fresh liver, and 3 Gm. autolyzed yeast. The mineral component provided per day calcium 50 mg., phosphorus 40 mg., iron 15 mg., copper 1.5 mg., iodine 0.1 mg., manganese, magnesium and zinc 1 mg. each.

RESULTS

A high incidence of nutritional deficiency occurred among the boys studied in this series. This was especially true of lesions of slight or moderate severity, although a surprisingly large number of severe glossitides (classifiable as frank pellagra) occurred in the population of this institution. Thus, fifty per cent of the boys showed slight glossitis, twenty-five per cent moderately severe glossitis, and fifteen per cent severe glossitis. The incidence of other lesions was lower, gingivitis about sixty-seven per cent, and cheilosis nineteen per cent. A majority of the boys had symptoms referable to the nervous system, such as excessive fatigability, hyperirritability, insomnia, headaches, memory defect for recent events, peripheral neuritis and repeated muscle cramps.

There was little correlation between the incidence and severity of the lesions and the duration of residence

*From the Endocrine Laboratory and Clinic, Beth Israel Hospital, New York 3, and the Psychiatric Clinic, The Children's Village, Dobbs Ferry, N. Y.

Submitted Sept. 13, 1946.

†Aided by a grant from the U. S. Vitamin Corporation.

††Vi-Syneral Capsules and Poly-B Syrup, generously supplied through the courtesy of the U. S. Vitamin Corporation.

Chart I: Incidence of Signs and Symptoms of Nutritional Deficiency at First Examination

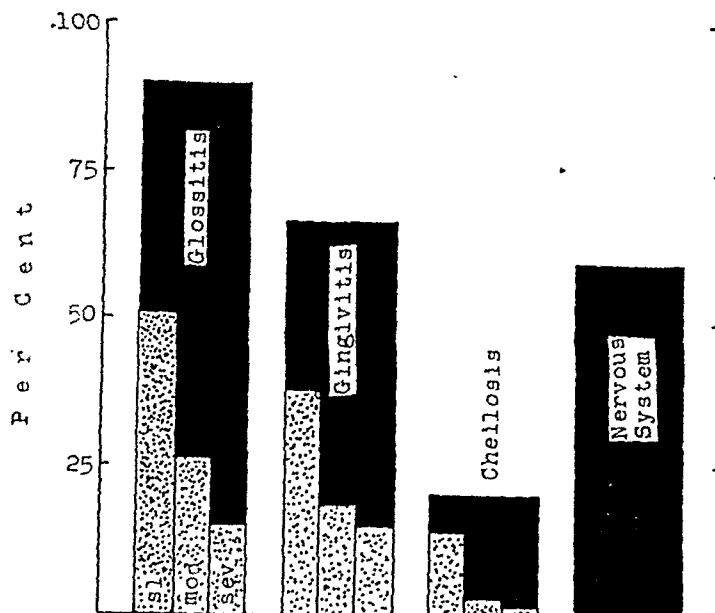
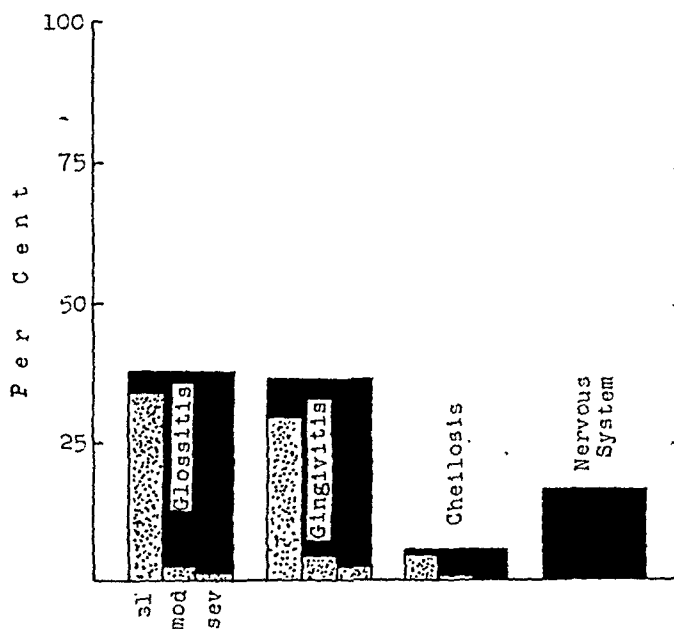


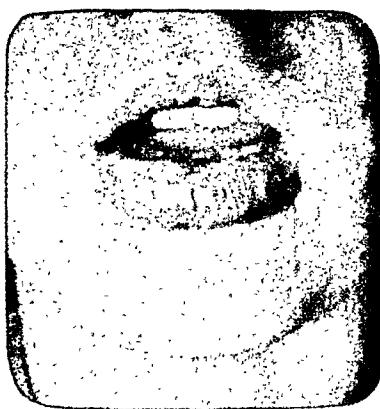
Chart II: Residual Incidence of Signs and Symptoms of Nutritional Deficiency after Treatment (Average Duration 3.7 mo. - Range 3 wks. to 7 mo.)



in the institution, although striking exacerbation of lesions was observed during the period of the study, when therapy was not followed (see Figs. 6, 11 and 12). Likewise, there was little correlation between the incidence or severity of the lesions and previous economic status or geographic origin. However, there appeared to be a definite increase in the severity of signs and symptoms of deficiency with increasing age. This is in agreement with the known tendency of un-

treated nutritional deficiency to be chronic and cumulative.

The major part of the food at this institution is prepared at a central commissary, the remainder is cooked in the individual cottages. Analysis of the prescribed diet at the institution for a period of several months during the investigation indicated that the daily lists prepared by the dietitian, if fulfilled, would have provided at least the minimal daily requirement of all

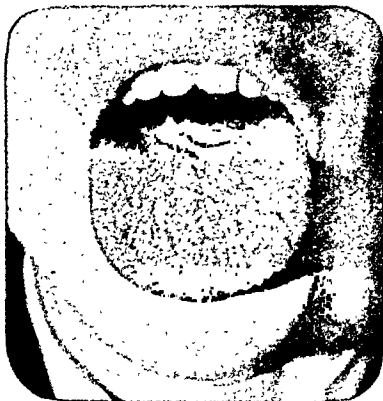


A



B

Fig. 1.—R. M., age 14 (No. 100). a. Cheilosis involving whole of lower lip. b. Improvement in cheilosis after 4½ months of therapy.

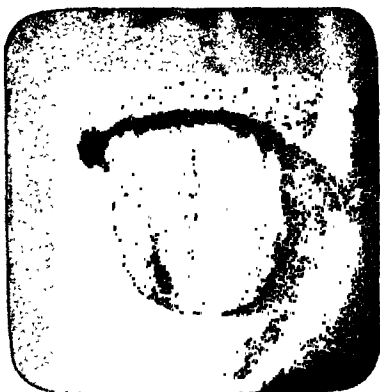


A

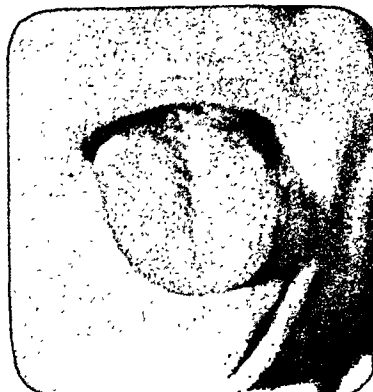


B

Fig. 2.—F. M., age 17 (No. 118). a. Fairly severe atrophic glossitis, with fissuring, atrophy and inflammation (dark areas). b. Virtually complete healing of glossitis, except for the two transverse fissures at the base (which are shallower), after 2 months of therapy.



A

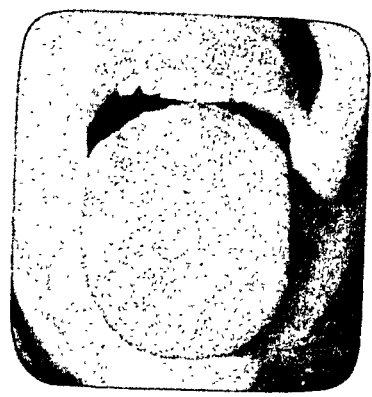


B

Fig. 3.—R. H., age 16 (No. 65). a. Glossitis with lingual edema (note indentations from teeth on the right margin). b. Considerable improvement of the glossitis after 5 weeks of therapy.

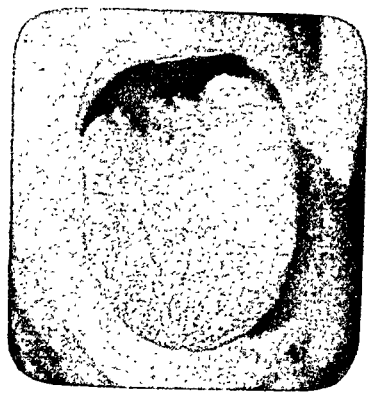


A



B

Fig. 4. — F. M., age 14 (Fig. 5, No. 120). a. Glossitis at first examination. b. Complete healing of tongue after 2½ months of nutritional therapy. (See also Fig. 16.)

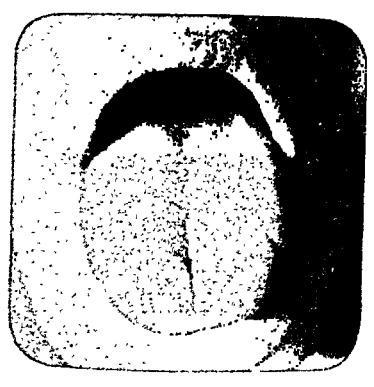


A

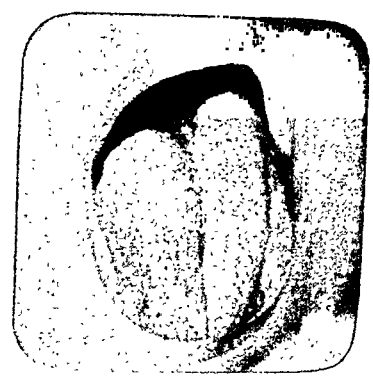


B

Fig. 5. — T. D., age 15 (No. 32). a. Initial glossitis. b. Virtually normal lingual surface after 1 month of vitamin therapy.



A



B

Fig. 6. — D. R., age 16 (No. 148). a. Moderate glossitis at first examination. b. Illustrating exacerbation of lesion after 3 months with only occasional and irregular therapy; there is some improvement in appearance of central portion of tongue but complete papillary atrophy along lateral margins. (Cf., Figs. 11 and 12.)

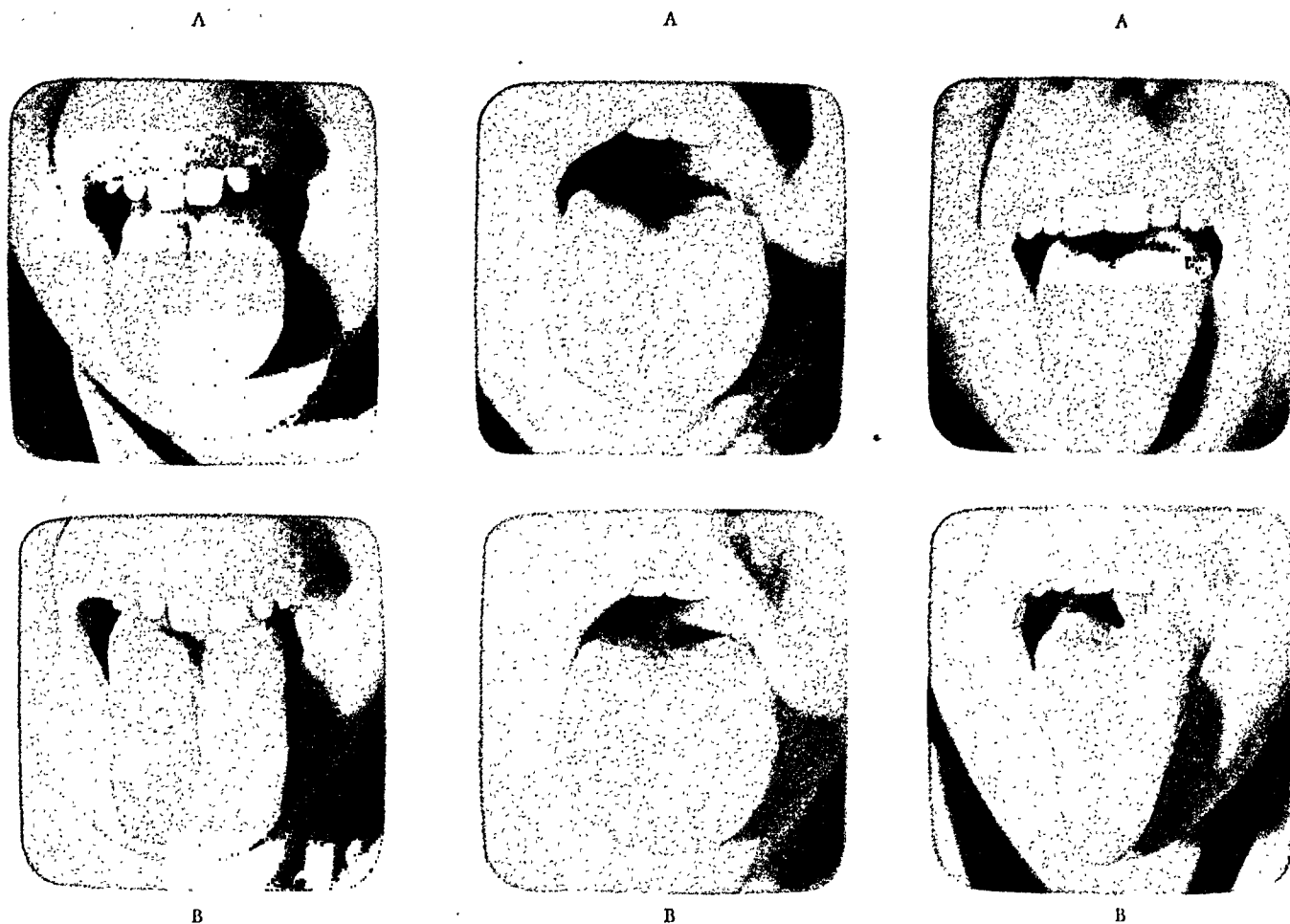


PLATE I.

Fig. 7.—V. H., age 11 (No. 72). a. Severe glossitis with sharply demarcated area of atrophy on patient's left. b. Improvement in lingual surface after 2 months of therapy.

Fig. 8.—T. S., age 15 (No. 156). a. Severe atrophic glossitis. Note sharply demarcated area of atrophy in anterior portion. b. Healing of glossitis after 5 months of nutritional therapy.

Fig. 9.—J. C., age 11 (No. 19). a. Severe atrophic glossitis with sharply demarcated area of atrophy on patient's right. b. Glossitis largely healed after 4½ months of therapy.

the known nutritional elements. However, both careful questioning of the boys themselves and evidence derived from records of weight during the study, indicated that major deviations from the prescribed diet occurred regularly, that there was considerable variation from cottage to cottage in the foods individually prepared, and that the caloric value of the diet was not adequate for the most part to permit the gain in weight normally concomitant with growth. Protein foods appeared to be especially deficient, mainly because of war-time shortages.

However, even had the diet been optimal, it would not have been sufficient to heal the lesions of deficiency already evident, since this requires at least from five to ten times the amount of the vitamin B factors than it is possible to obtain in a normal diet (10).

Comparison of Charts I and II, and of the "before and after" pictures in Figs. 1 to 18, shows the effect of fairly intensive nutritional therapy on the indications of nutritional deficiency. Not only was there a sharp reduction in the incidence of the various lesions, but an even more striking shift in the severity of those

remaining. Chart II illustrates the fact that all but a few of the residual lesions could be classified as slight. In the experience of one of us (M.S.B.), had it been possible to treat the patients on an individual basis, varying the amount and kind of therapy to suit the individual case, even better results would have been possible in the time limits of the study. As it was, even with the complications afforded by variations in therapy resulting from individual aberrations of the boys themselves and from variations in their supervision from cottage to cottage, it is evident that mass therapy of the type here practised can be of great value.

Aside from changes in the avitaminotic lesions, recorded for the most part photographically, an effort was made to assay subjective changes. Leading questions were carefully avoided. The most common retort to the question as to whether any change had been noted, was: "I don't get so tired", "I have more pep", "I'm not so sleepy during the day", "I want to go out and play now", or variants on that theme. Others reported that they slept better, were "not so nervous", or had fewer headaches. These responses, admittedly

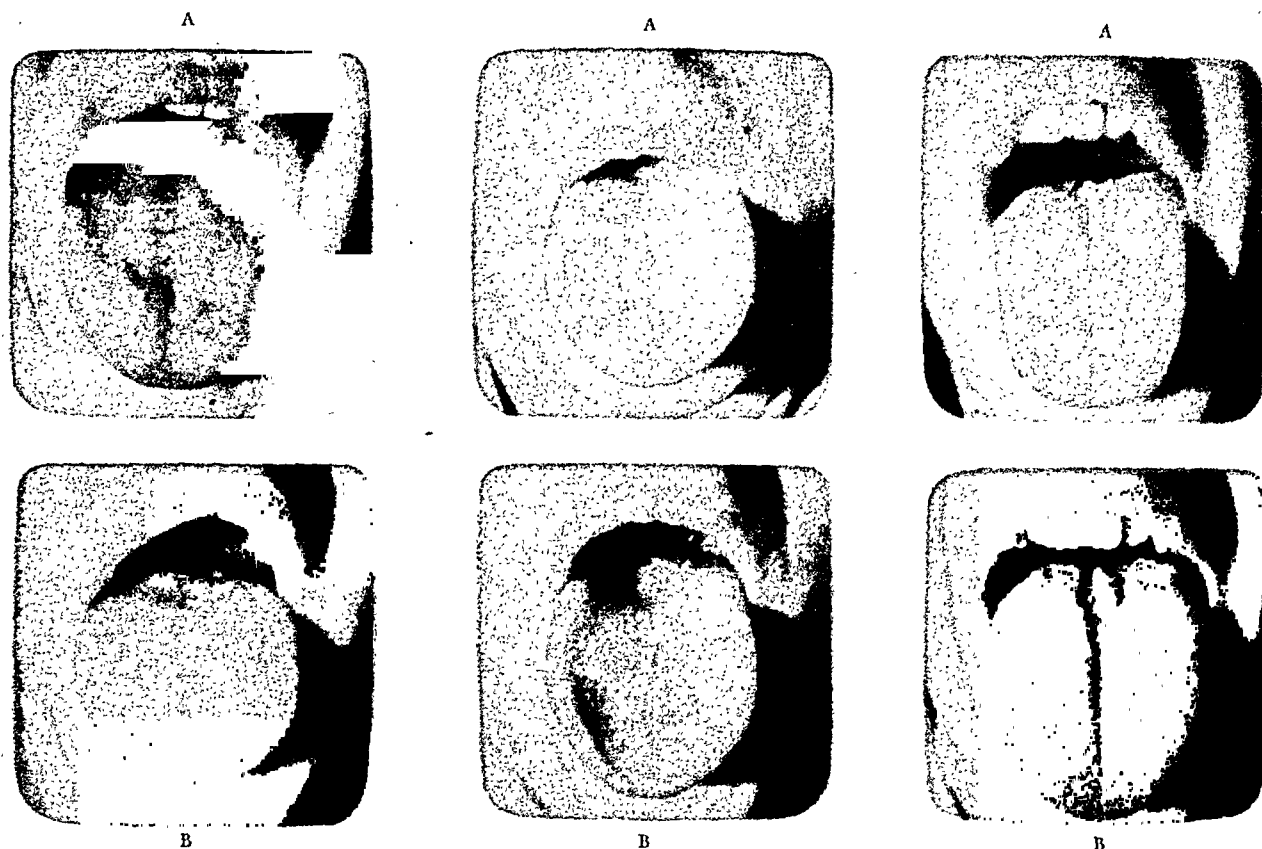


PLATE 2

Fig. 10.—V. W., age 16 (No. 176). a. Fairly severe glossitis at first examination. b. Complete healing of tongue after 3 months of vitamin therapy.

Fig. 11.—J. L., age 14 (No. 91). a. Minimal glossitis at first examination. b. Severe exacerbation of glossitis 6 months later, without therapy.

Fig. 12.—R. B., age 17 (No. 17). a. Beginning glossitis at first examination. b. Six months later with little or no therapy; severe exacerbation of glossitis.

difficult to evaluate because many of the boys were severe neurotics, nevertheless appear to be valid. This is especially so as the phenomena concerned are definitely known to be affected by nutritional therapy, and because the subjective changes took place along with objectively visible improvement in the lesions.

DISCUSSION

A number of interesting problems are posed by the high incidence of avitaminotic lesions in so young a group of the population. Recognition of these lesions in casual medical examinations is not usual, and mild lesions of the tongue, for instance, are so common that they are accepted as "normal".

In the course of a study of certain endocrine disturbances related to nutritional deficiency (11, 15) one of us (M.S.B.) began about five years ago routine recording by Kodachrome photography of the various aberrations in the morphology of the tongue. Further photographs were made at intervals during nutritional therapy and in its absence. As a result of this study, which involved observations on hundreds of subjects, it became apparent that many of the changes thought previously to be simple aberrations of the "normal", were in reality reflections of more or less serious nutritional deficiency,

involving for the most part serious disturbances in hepatic function. Striking changes were observed in these tongues under therapy along with improvement in the functional disturbances. Thus it was possible to set up criteria for the appearance of a healthy lingual surface.

The study reported here supplemented, on a younger group, the original observations. The deviations from the healthy state were of precisely the same types and showed the same responses to therapy (see color plates 1 to 3; Figs. 7 to 10 and 13). Many of the lesions cannot satisfactorily be reproduced in black and white because changes in color, some of them quite subtle, are extremely important to their recognition.

Does the occurrence of indications of nutritional deficiency in ninety per cent of the group of children examined, reflect a similar deficiency in the general population? It is not improbable that it does, even though special circumstances existed in the case of this group which may not be equally operative in the population as a whole. Numerous investigations of this subject by many workers in many parts of the North American Continent, and elsewhere, have all indicated an extremely high incidence of nutritional deficiency.

It is probable that many of the boys in the group

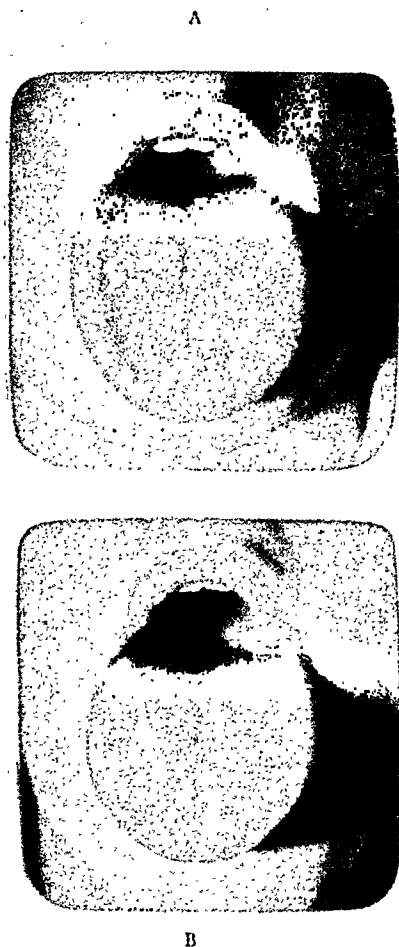


Fig. 13.—P. L., age 13 (No. 92). a. Moderately severe glossitis with scattered fissures. b. Note healing of all except central fissure after 5 months of therapy.

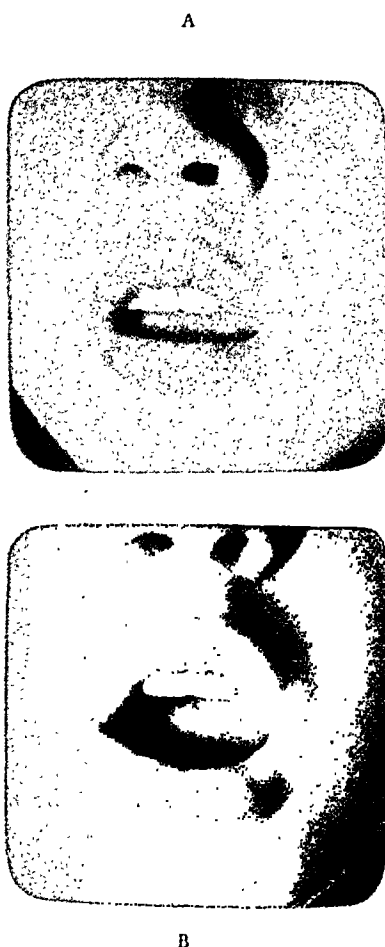


Fig. 14.—R. M., age 10 (No. 112). a. Cheilosis involving angles of mouth and both lips. b. Cheilosis healed after 6 months of therapy.

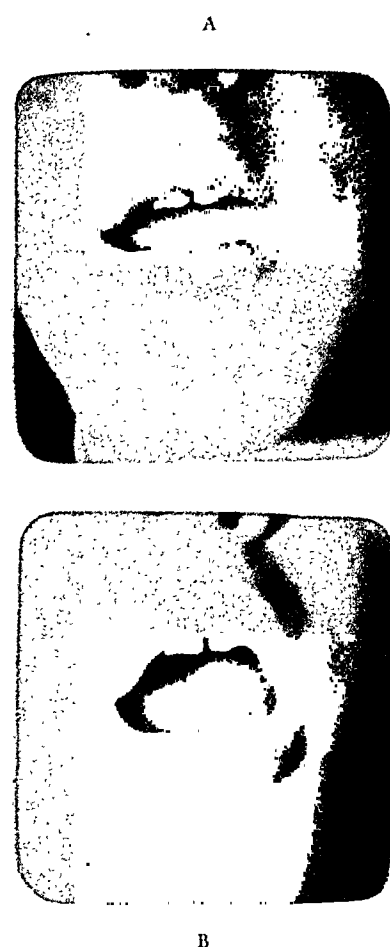


Fig. 15.—J. B., age 11 (No. 9). a. Cheilosis involving left angle of mouth. b. Lesion healed after 7 months of therapy.

PLATE 3

here studied, started life with the handicap of a minimal or sub-minimal deficiency acquired in utero, for studies on nutrition during pregnancy have revealed a woeful inadequacy of diet in almost all pregnant women regardless of economic status (16, 18). After birth, with variations in diet and with operation of the numerous conditioning factors, the nutritional status slowly deteriorates (unless supportive therapy is instituted and is maintained thereafter). The cumulative deterioration in nutritional status with time has been thought to be mainly a problem for adults and to have especial significance only for geriatrics. But, at least during the period of the study reported here and, quite obviously for some years before, factors were operating to produce a significant deterioration in the nutrition of this group of children, a defect that was apparently progressive, as both the incidence and severity of the lesions were the greater, the older the subjects. As the detectable avitaminotic lesions reflect functional changes of far-reaching significance, not the least of which occur in the nervous system, handicaps thus imposed upon the growing child and adolescent cannot be lightly dismissed.

Excessive fatigability, hyperirritability, emotional in-

stability, headaches, memory defects, insomnia and the like (superimposed to a certain extent in the case of the boys in the group studied here, on similar phenomena of neurotic origin), can prove insurmountable obstacles in the development of any child.

In a recent report concerned with effects on the nervous system of administration of a supplement of thiamine to institutionalized children, Harrell (9) has demonstrated, under unusually well-controlled conditions, that even partial nutritional therapy of this type can have remarkably beneficial effects. Striking improvement over a control group occurred in visual acuity and in the performance of a variety of tests designed to assess the higher cerebral functions, simply on addition of thiamine to the diet. And there was definite deterioration in these abilities when the supplementary thiamine was withdrawn. (Favorable effects on growth also occurred in the thiamine-supplemented group). Thus, impairment of intellectual processes in nutritional deficiency, may be added to the handicaps already mentioned.

It may be noted in Charts I and II that the gingivitis showed the slowest response to therapy of all the

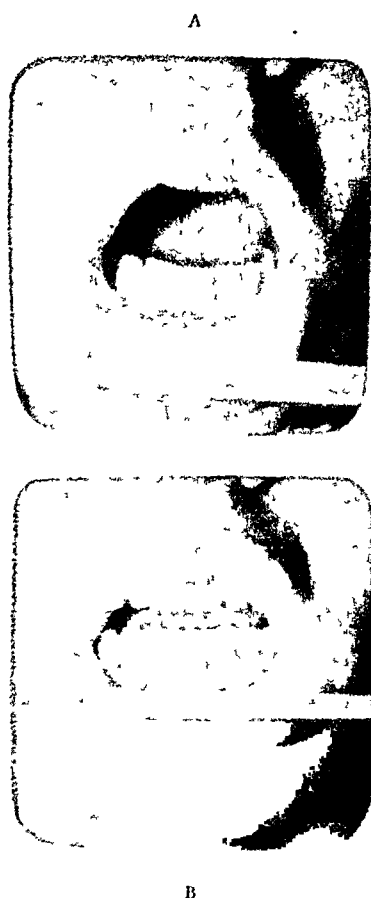


Fig. 16 — F. M., age 14 (No 120). a Severe gingivitis on initial examination. b Improvement after 3 months of nutritional therapy.

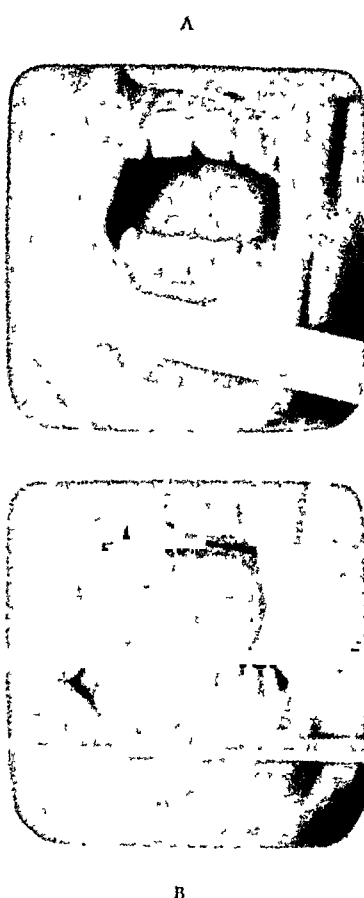


Fig. 17 — N. P., age 15 (No 132). a. Severe gingivitis at first observation. b Upper half healing of upper gums after 1 month of therapy. Lower half: Moderate improvement but persistence of gingivitis in lower jaw after 5½ months of therapy.

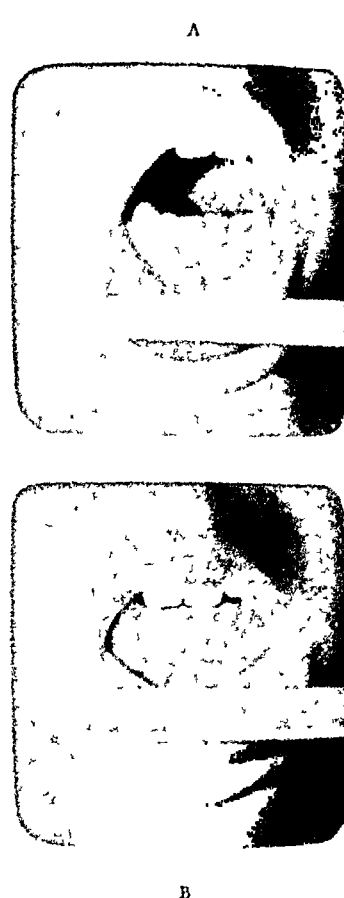


Fig. 18 — T. M., age 10 (No 101). a Gingivitis on first examination b Improvement after 2½ months of therapy

PLATE 4

lesions, an observation in agreement with the experience of one of us (M.S.B.) in treating adults. Nevertheless, a considerable number of these lesions were healed completely during the period of the study. Gingivitis of the type observed is not solely scorbutic or pellagrous in character, and does not respond to ascorbic acid or niacinamide alone or in combination, but does respond slowly to *complete* nutritional therapy containing the available pure vitamins, plus an adequate natural source, preferably liver. In adults complete healing has often required intensive therapy for from many months to a year or more. It is reasonable to assume that further intensive therapy in these boys would eventually have led to disappearance of the residual lesions.

The investigation reported here supports the view that nutritional deficiency may occur in children and adolescents much more commonly than previously supposed, and that examination for and treatment of indi-

cations of avitaminosis should have high priority in routine medical care.

SUMMARY

Examination of 183 boys in a children's institution, revealed an unexpectedly high incidence of signs and symptoms of nutritional deficiency. Approximately ninety per cent had glossitis, sixty-seven per cent had gingivitis, nineteen per cent had cheilosis and sixty per cent had avitaminotic symptoms related to the nervous system. Routine nutritional therapy with the vitamin B complex, together with ascorbic acid and vitamins A, D and E, of all but a few of this group, during a period of seven months, led to a complete disappearance of the indications of deficiency in most of those affected, and improvement in all but a few of the residual group. This study supports the view that examination for and adequate treatment of the stigmas of nutritional deficiency should have high priority in routine medical care.

TABLE I. INCIDENCE AND SEVERITY OF AVITAMINOTIC LESIONS AND EFFECTS OF THERAPY

No.	Pt.	Age	Home	Residence in	Ht. (in.)	Wt. (lbs.)	Glossitis	Gingivitis	Cheliosis	Splitting Finger-nails	Skin Lesions	Conjunctivitis	Excessive Fatigability	Hyper- irritability	Insomnia	Memor-	Impairment	Headaches	Neuritis	Therapy per day	Duration	Subsequent Ht. Wt.	Results
9	JB	11	Conn.	8 mo.	56 1/4	83	+	++	+++	+	+	+	++	+	0	0	0	0	0	0 B comp. syr. 15cc vit.-min. suppl.	6 1/2 mo.	57 1/2, 82	All lesions completely healed; much less fatigue.
17	RB	17	N.Y.St.	12 mo.	67 1/4	130 1/4	+	+	0	0	+	+	0	0	0	0	0	0	0	0 Virtually no therapy	6 mo.	68, 131	Exacerbation of glossitis.
19	JC	11	Ill.	2 mo.			+++	+++	0	+	+	+	+	+	+	+	+	+	+	0 B comp. syr. 15cc vit.-min. suppl.	6 mo.	56, 80	Glossitis healed, occurred when therapy stopped; gingivitis and other signs healed; striking improvement in subjective symptoms and in behavior.
32	TD	15	N.Y.C.	4 1/2 yrs.	68 1/4	148 1/2	+	+	0	0	+	0	+	0	0	0	0	0	0	0 B comp. syr. 15-45 cc; vit.-min. suppl. (irregularly)	4 1/2 mo.	69 1/4, 153	Glossitis and gingivitis improved but latter still present; fatigability less on therapy.
65	RH	16	N.Y.St.	14 mo.	65 1/4	113	+	+	0	+	+	+	0	0	0	0	0	0	0	0 B comp. syr. 15-20 cc vit.-min. suppl. (occass. 2x)	6 wks.	65 1/4, 115	Glossitis improved; gingivitis healed. Other signs cleared.
72	VH	11	Ohio	14 mo.	62	108 1/2	+++	+++	0	0	0	0	++	++	++	++	++	++	++	0 B comp. syr. 15 cc vit.-min. suppl.	2 mo.	62 1/4, 108 1/2	Very marked improvement in all signs and symptoms; no longer "jumpy and nervous"; sleeps better; less tired.
91	JL	14	N.Y.St.	3 mo.	65	125	+	+++	0	0	0	0	0	0	0	0	0	0	0	No therapy	5 mo.	65, 122	Glossitis severe.
92	DL	13	N.Y.St.	4 mo.	65	111	++	0	0	0	0	0	0	0	0	0	0	0	0	0 B comp. syr. 15 cc vit.-min. suppl.	5 mo.	65, 119	Glossitis healed.
100	RM	14	N.Y.C.	3 mo.	66	139	+	+++	+++	+	+++	+	+	+	+	+	+	+	+	0 B comp. syr. 15cc vit.-min. suppl. (irregularly)	7 mo.	67, 128 1/2	Glossitis and cheliosis much improved; gingivitis moderately improved; subjective disturbances still severe.
101	TM	10	N.Y.St.	6 mo.	55 1/4	80	+++	++	+	+	0	+	++	+	0	0	0	0	0	0 B comp. syr. 15cc vit.-min. suppl.	6 1/2 mo.	57, 80	Cheliosis healed; glossitis much better; gingivitis moderately improved; marked subjective improvement; less fatigue.
112	RM	10	Mass.	8 mo.	54 1/2	73 1/2	0	0	+	+	+	0	0	0	0	0	0	0	0	0 B comp. syr. 15cc vit.-min. suppl.	6 mo.	56, 78 1/2	Cheliosis healed; persistent epidermophytosis of face; muscle cramps persist.
118	FM	17	N.Y.C.	10 mo.	67 1/4	124 1/2	++	+	0	+	+	+	++	+	0	0	0	0	0	0 B comp. syr. 10-45cc vit. suppl.	2 mo.	67 1/4, 124	Marked improvement in glossitis; skin lesions all healed except residual slight acne; gingivitis slight; marked lessening of fatigue.
120	FM	14	N.Y.C.	5 mo.	65 1/4	151	+	+++	0	0	0	0	+	+	+	+	+	+	+	0 B comp. syr. 10-45cc vit.-min. suppl.	5 mo.	66, 143	Glossitis and gingivitis markedly improved; "more energy"; "nervous better"; took 500 cc B complex syrup and 24 vit.-min. supplement in one dose on a dare! — no ill effects.
132	NP	15	N.Y.C.	4 mo.	66 1/2	136	++	+++	0	0	+	+++	0	0	0	0	0	0	0	0 B comp. syr. 5-10cc only	5 mo.	66 1/2, 137	Glossitis and gingivitis improved.
148	DR	16	N.Y.St.	2 yrs.	70	159	++	0	0	0	+	+++	0	0	0	0	0	0	0	0 B comp. syr. 5cc vit.-min. suppl. (irregularly)	3 mo.	70 1/4, 155 1/2	Only occasional therapy; developed complete papillary atrophy lateral borders of tongue.
156	TS	15	N.Y.C.	5 mo.	69	141	+++	++	0	0	+	+	+	+	+	+	+	+	+	0 B comp. syr. 15cc vit.-min. suppl. (irregularly)	5 mo.	69, 137	Glossitis healed; slight gingivitis; feels "more peppy."
176	VW	16	N.Y.St.	2 mo.	68 1/4	170	++	+	+	0	+	+	+	+	+	+	+	+	+	0 B comp. syr. 5-15cc vit.-min. suppl.	6 mo.	68 1/4, 154	No glossitis, gingivitis or cheliosis; less fatigue; sleeps better; less irritable.

*Owing to space limitations, this table has been abbreviated to include data only on the boys whose photographs are here reproduced. The complete table appears in the authors' reprints.

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ACKNOWLEDGMENT

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An Instructive Case of Treated Hepatic Disease, With a 27 Year Follow-up.

By

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PHILADELPHIA, PA.

I FIRST SAW Mr. X. on October 1, 1919. He had been referred to me by a surgeon who felt that a diseased gall bladder was responsible for his symptoms. For 2½ years I had been interested in studying the possibility of duodenal tube drainage of the biliary system as a diagnostic and therapeutic procedure (1).

When 10 years of age Mr. X. had had a severe and prolonged case of typhoid fever during which he had suffered two attacks of pain suggestive of cholecystitis. Since then he had had recurrent attacks of mild jaundice. These cleared after calomel, to which he had become addicted because it helped, he thought, to control what he called "bilious attacks, constipation, auto-intoxication and acne." At such times he became mentally dull and had difficulty in concentrating on his work as an advertising writer. He rarely used alcoholic beverages.

A diagnostic drainage was done which failed to incriminate his gall bladder. His liver bile, however, was definitely pathological, being considerably darker and thicker than normal. It was turbid, and contained much flocculent debris. Microscopically it showed bile stained mucus, exfoliated bile stained short columnar epithelium, only a few pus cells, but many bacteria. Cultures, however, were sterile. This study was repeated three times with similar findings save on one occasion when there was a suggestion of a low grade catarrhal cholecystitis. An X-ray study by Dr. Willis Manges failed to support this. Cholecystography had not yet been introduced. Liver function tests were crude and of little value.

Submitted Nov. 24, 1946.

As a result I reported to the referring surgeon that I did not feel that this patient required an operation. As I look back over the years it is possible that I may have been influenced by the fact that his appendix had been removed in 1917 and his gall bladder had been digitally explored and stated to be normal.

The surgeon then requested that I take charge of Mr. X.

During 1920 he was given 15 duodeno-biliary drainages. One in January; two in February; one in March; three in April; four in May; and one each in June, July, August and September.

Mr. X. improved somewhat, with less sense of biliousness and bitter taste in mouth, less sallowness and faint scleral icterus. His dull headaches decreased as his bowel elimination improved. It was provoking and despite this transient improvement, discouraging to both of us to see him relapse so frequently.

On June 9, 1920, Dr. Russell Richardson had perfected a bile culture flask and a new culture medium, and for the first time he reported a pure culture of streptococcus hemolyticus from Mr. X's B bile. All previous cultures had been sterile, although myriads of bacteria were seen in the many drainage sediments. Dr. Richardson prepared a vaccine which was administered during subsequent weeks.

In November, 1920, Mr. X. moved to a new position in New York City and I lost track of him for 14 months. He reappeared in Philadelphia and was emphatic in his belief that his gall bladder was responsible

for his ill health. He insisted that it should be removed. I agreed and made the necessary arrangements. I was anxious to see what his gall bladder and liver would look like. This was the only way to learn how accurate biliary drainage might be as a diagnostic procedure.

THE OPERATIVE FINDINGS AND COMMENTS THEREON

On February 22, 1922, Mr. X. was operated upon by Drs. Duncan Despard and Leslie Mulford. The fundus of the gall bladder was adherent to the hepatic flexure and the neck of the gall bladder was adherent to the duodenum. Both adhesions suggested the congenital variety and were so fine and so delicate as to be easily broken by the finger. The foramen of Winslow was readily patulous, but the head of the pancreas was hard. The liver was somewhat enlarged; its edge and surface were hard. It was mottled and scarred with connective tissue to such an extent that it resembled the laminations seen when plate glass is splintered along its edge. All four doctors at the operating table considered it to be cirrhotic. Dr. Despard felt it unwise to remove a portion for biopsy. The gall bladder itself appeared normal, its walls were not thickened and it readily collapsed on simple handling. No stones could be felt. There was no evidence of ulcer.

I think the surgeons were surprised that there was no evidence of gall bladder disease. But I confess to a feeling of elation that my diagnostic test had proved reliable.

After consultation Dr. Despard decided to remove the gall bladder on the ground that the patient was counting heavily on his belief that it was the cause of his disability, and so might derive more psychic benefit therefrom than if his abdomen was merely explored and closed with nothing surgically done. Having made this decision Dr. Despard was forced to a second one, namely that it was wiser—and perhaps it was—not to tell Mr. X. about the condition of his liver.

Cultures taken from the gall bladder bile at operating table were sterile, as were those later taken after scraping its mucous membrane. This made it questionable whether the positive culture previously obtained from the biliary drainage represented infection of the bile. The pathologist reported a normal gall bladder. Mr. X. made an uneventful recovery.

I put him on orthodox management for cirrhosis of the liver as outlined in text books of that period. What a "do little program" it was! There was nothing left for me to do except to wait for the break in his health that was bound to occur if he had true cirrhosis.

COMMENT

Meanwhile, I reviewed Mr. X's records carefully and I hit upon a clue. It was evident that his relapses were *less frequent* in ratio to the frequency of biliary drainage and vice versa. On reflexion, this seemed natural. I surmised that he had a sick liver, only partially functioning, and probably hampered by clogged

intra- and extrahepatic ducts. It was noted that when his drainages were scheduled more frequently, that is several times a month, that his liver bile improved in color and consistency; it lost its turbidity and increased in amount; and the pathological debris was definitely less. Coincident with this his symptoms were lessened. Conversely, when the drainage interval was lengthened his symptoms recurred, and coincidentally the pathologic gross and microscopic evidence increased. It seemed therefore, that the irregularly scheduled short drainages he had been given were not sufficient to drain out the poisonous products that had accumulated in his liver and ducts. We were not keeping ahead of the rate of their production and the progress of his disease. If that were so, it was a good clue to follow.

So I planned more intensive drainage of the liver such as was subsequently to become known as Continuous Biliary Drainage. Its technic has been twice described. (2). (3). This procedure was designed to imitate, so far as possible, surgical drainage of the liver by choledochostomy in a patient with an unobstructed common duct.

It brought back to mind observations made ten to fifteen years earlier when the writer was working in the Lankenau Hospital, presided over by John B. Deaver. It was in the era of cholecystostomy and choledochostomy. These operations helped for a while but the toxic symptoms soon returned after the cholecystostomy or choledochostomy was closed and bile again was allowed to enter the intestine.

These, and other, observations led up to the conception and report of three vicious circles that can be recognized in biliary tract disease (4). This indicated the great advantage that *external* drainage of toxic bile has over *internal* drainage. It should effectually have hushed the clamour of those who cried: Why put a patient to the discomfort of swallowing a duodenal tube in order to introduce epsom salts or other choleagogue? Why not simply let him swallow the medicine and get as good result by internal drainage?

The answer is: One does not get as good result because of the vicious circles to which you have been referred because there is not space to reincorporate them in this article.

THE BREAK IN HEALTH SOON CAME

Mr. X. returned to Philadelphia in the fall of 1924. He was disappointed at the result of his operation. He still had his recurring biliousness, headaches, mild jaundice, and toxic disability despite calomel courses periodically and a biliary drainage (which he had learned to give himself) about once a month. He had noticed that too frequent use of meats, especially the red variety, produced increased sallowness, a sense of hebetude and a general below par feeling. At such times he noticed that his bowel movements were lighter in color. He thought he was "slipping."

And indeed he was. He had lost 20 pounds, to 119, more noticeably in arms and legs. His liver had gradually enlarged—the palpable edge was hard. There

was no ascites. Telangiectases were present along the right costal margin.

By this time he had received whatever psychic benefit had accrued from his cholecystectomy, as little as it appears to have been. So he was told the truth about his liver. He took it very well. In fact he appeared relieved that something definite had been found that accounted for his feeling so bad. I reported to him some of the observations I had made from restudying his drainage records. I showed him the outline of the plan of continuous biliary drainage and asked him if he would be the first person to try it. He agreed to do so.

He entered hospital on September 22, 1924, weighing 121 $\frac{1}{4}$ pounds and was discharged on October 11

date. For a dozen years or more he worked a citrus grove which he had purchased near Orlando. Since disposing of this he has led an outdoor life in developing a new lake-side home and planting trees and a lovely garden. This wholesome, outdoor exercise has doubtless contributed to his excellent recovery.

But the early years were not easy. He had a good many ups and downs. He was, and is, spasmophilic—spastic pylorus, irritable duodenum, spastic descending sigmoid colon. Particularly annoying was the regurgitation of bile into his stomach. One reason for this was that after removal of his gall bladder he never regained physiological control of Oddi's sphincter. On the many occasions it was tube tested, bile was always found flowing into the duodenum, and with "duodenal

CHART I

Date 1924		A. M.	Recovery of bile mixture			
			P. M.	Day Total	Overnight Total	Total
Sept. 21	Drainage 9—11:10 A. M.	275		275	1100	1375
Sept. 24	Drainage 8 A. M. to 2 P. M.	700		700		700
Sept. 25	Drainage 8:10 to 12 M.	395		395		395
	Full diet tray at 12:30. A. P. M. breath Stomach washed, large amount food block. Removed, cleaned, re-allowed. Again food blocked. Removed for the night.					
Sept. 26	A. M. Drainage, 3 stimulations, plus 3 jejunal feedings in P. M.	315	195 + 425	915	1800	2715
	Wt. 117 $\frac{1}{4}$					
Sept. 27	A. M. Drainage plus 3 feedings in P. M.	475	515 + 470	1470	790	2240
Sept. 28	Jejunal feeding plus A. M. drainage	550		550		550
Sept. 29	Rest day. Full diet					2810
Sept. 30	A. M. Drainage plus 3 feedings in P. M.	410	320 + 410	1130	1750	2910
Oct. 1	Jejunal feeding plus A. M. drainage	245		245		245
Oct. 2	Rest day. Full diet					3155
	Wt. 120					
Oct. 3	A. M. Drainage plus 3 feedings in P. M.	575	505 + 505	995	1350	2335
Oct. 4	Jejunal feeding plus A. M. drainage	290		290		290
Oct. 5	Rest day. Full diet					2625
	Wt. 121 $\frac{1}{4}$					
Oct. 6	A. M. Drainage plus 3 feedings in P. M.	310	345 + 505	1220	1450	2670
Oct. 7	Jejunal feeding plus A. M. drainage	325		325		325
Oct. 8	Rest day. Full diet					2995
	Wt. 122 $\frac{1}{4}$					
Oct. 9	A. M. drainage plus 3 feedings in P. M.	335	395 + 310	1040	1500	2340
Oct. 10	Jejunal feeding plus A. M. drainage	210		210		210
Oct. 11	Rest day. Full diet. Treatment completed					2770
	Wt. 123					
		5470	4550	10,020	9740	19,760

weighing 123 pounds, despite the fact that during that period we had removed nearly 5 gallons (19,760 c.c.) of bile mixture which weighed 40 pounds. This was recovered in approximately 133 drainage hours, over a period of 18 days, only 14 of which were drainage days.*

THE PRELIMINARY FOLLOW-UP, 1927-1932

It was suggested to him that he might have a better chance of recovering health if he resigned his indoor occupation in New York and could find an occupation outdoors that would interest him, particularly in a climate that would be more uniformly warm than cold. It was pointed out that at early age he could make such a radical break with less difficulty than if he waited until later.

After due consideration Mr. X. agreed to this. He tried California for a period, but finally chose Florida, in February of 1927, where he has lived up to present

delirium," it was regurgitated into his stomach. This produced his nausea and bitter taste and was best relieved by gastric lavage and biliary drainage. These symptoms were always exaggerated by upper respiratory colds to which he was abnormally sensitive. Periods of irregularity in bowel function—constipation, and sudden brisk attacks of diarrhoea were also troublesome.

When put on his own, after becoming technically proficient in duodenal intubation, he was instructed to take one short morning drainage once a week and one overnight drainage once a month. One very good characteristic possessed by Mr. X. was his persistence in his desire to get well. Although he was more conscientious than most in his semi-annual or annual appearances or reports, a review of his records indicates that he took less technical treatments than was recommended.

It was interesting to find that Mr. X. had by personal experience antedated the dietetic knowledge so rapidly

*See Chart I

growing by animal experimentation, and had found that for his sick liver a high carbohydrate diet, relatively low in protein and fat, was best tolerated. If the gall bladder has been removed the fat can be still further reduced. An avoidance of roughage was also advised.

Medicinally, at first pancrobin and senna-agar fruit paste and occasionally calomel were used, plus antispasmodics and sedatives. In 1933 decholin tablets and psyllium seed in the form of Konsyl appeared to do better. Still later sugar and salt tablets and various vitamin formulae were prescribed.

THE LONG FOLLOW-UP, 1933-1946

There are two episodes worthy of report. The first occurred in June 1933; the second in May 1937.

On June 23, 1933 Mr. X. reported in person from Florida after a year's absence. It may be of interest to include certain notes made at this series of visits. He states that the past 12 months have not been as good as the preceding 12. He attributes this to an upper respiratory cold involving his ethmoid sinuses which "hung on endlessly throughout the winter." As a result of this added infection he noted loss of strength and endurance, increased spastic constipation, less well controlled by belladonna. At one period during the winter headcold he became definitely jaundiced for 2 weeks. This cleared gradually after a calomel course. This is the characteristic result of any added infection hitting the patient's "weak spot." During the year he has taken only 3 short morning drainages and approximately 50 gastric lavages to remove regurgitated bile.

His general "let down feeling" was accounted for by a low blood sugar of 66 mg. Non protein nitrogen has increased to 58.8 mg., with uric acid and urea nitrogen remaining at normal values. Icterus index has dropped to 10.5 units as contrasted with 30 units in 1927. Quantitative bilirubin was 1.07 mg. as contrasted with 1.6. Direct van den Bergh reaction formerly negative is now biphasic. In 1933 Brom dye liver function test (2 mgm. per kilo) at 5 mins. = 63% = slight increase

30 mins. = 2% = normal

60 mins. = 0% = normal

Urine urobilinogen 1 to 40.

Stool exam., soft formed, brown, mucus increased, occult blood negative. Microscopical poor fat conversion; excess striated and unstriated muscle fiber.

Wassermann and Kahn tests, negative.

Partial physical exam.: No scleral jaundice. P. 78. B. P. 116-78.

Lungs and heart satisfactory. Liver, upper border to percussion from 6 interspace to 1½ cm. below costal margin, where edge is barely palpable. Telangiectases, previously noted, have disappeared. Spleen is negative.

Mr. X. was given 10 gm. of glucose intravenously on June 23, 24 and 26. On the latter date blood sugar

had risen to 88 mg. Despite glucose injections on July 5 and 12, the blood sugar unexpectedly dropped to 66 mg. A 10 gm. glucose injection was given on July 19. When he returned on July 26 his blood sugar incredibly had increased to 211 mg.

This excited office comment. We feared a laboratory error. But this was not the case. Our skilled technician, Miss F. A. Keen, was sent to Jefferson Hospital to check their blood sugar standards with our office standards. Mr. X's blood sugar was rechecked by both standards, and further controlled by blood taken from two other patients, and both sets of standards were identical. With Mr. X's blood sugar at 211 mg. there was no spilling over of sugar in his urine by way of the renal threshold.

How can we interpret this extraordinary fluctuation? It suggested a disturbance in the glycogenetic function of Mr. X's liver, plus a possibility of a coincident pancreatic instability. Two interpretations were attempted. A. At one time the liver may be unable to extract the excess of blood sugar and to store it as glycogen. B. At another time the liver has unduly extracted blood sugar, but has failed to warehouse it as glycogen.

I have reported this episode at length because of its unusualness. It never has recurred within our observation.

When Mr. X. was next seen on September 15, 1933 his blood sugar was 85 mg.; a perusal of his lengthy record indicates that it never again fell below this level or rose higher than 110 mg.

The last episode worthy of report was the sudden development of a peptic ulcer, suggested clinically, and confirmed by X-ray in May, 1937 by Dr. Bernard P. Widmann who reports it as "prepyloric, associated with zonal gastritis and duodenitis, and an intense degree of colon spasticity." There were four potential causative factors.

Mr. X. has been subject to pylorospasm and to spasm of his colon since I first saw him in 1919. At that time he had an extragastric lesion type fractional analysis with high two hour acidity. Since then he has suffered much ill health.

His father died in late 1934 which was a severe blow to Mr. X. The long tedious job of settling this estate throughout 1935 tired him out and got him nervous and jittery.

During 1935 pyorrhoea, gingivitis and dental caries required several months of dental care.

Recently he had been in a serious automobile accident.

He was put on a rigid ulcer management program, with the first month spent resting in bed, and he has made a fine recovery.

FINAL NOTE

I saw a lot of Mr. X. in Winter Park, Florida, during the winters of 1944, 1945 and 1946, and at one period lived as his house guest for two weeks. I had

an opportunity to observe his daily life, his food, and work habits. He appears amazingly well 27 years after his liver was first suspected of being cirrhotic, and nearly 24 years since it was viewed at operating table. He leads a regular and healthful life, always taking an afternoon siesta. He puts in about 4 hours a day working on his garden, his shrubbery and lawn. He eats prudently and much the same food as other people eat. In recent years he has been able to tolerate increasing amounts of animal protein, chiefly lamb and beef. Rarely he may take a cocktail or a rum highball. His weight fluctuates between 145 and 155. He has taken no drainages in three years and only occasionally a gastric lavage.

In the spring of 1946 I suggested that Mr. X. should have a survey of the state of his liver functional capacity, and I referred him to Dr. Harry L. Bockus, formerly a student of mine, later a beloved colleague.

The very satisfactory report which concludes this narrative, emphasizes, as did the 25-year follow-up of Anna Ingber Penn, (5) the extraordinary capacity for recovery a severely damaged liver possesses, provided it is given a proper chance to recover, assisted by recent improvements in management.

June 29, 1946

Dr. B. B. Vincent Lyon
1930 Chestnut Street
Philadelphia, Pennsylvania

Dear Vincent:

I thank you for referring Mr. X. for an appraisal of the status of his liver. I will not review his past history with which you are so thoroughly familiar. Evidently he has had no complaints related to the liver for some years. I believe there was some question about the presence of a duodenal ulcer in 1937 although his description of symptoms at that time did not sound particularly typical. Since then, he has had only occasional slight heart burn.

The physical survey revealed nothing of moment; the blood pressure was a little low, systolic 90, diastolic 54; the cardiovascular survey otherwise was negative. I could make out no appreciable enlargement of the liver and the area of liver dullness seemed to be about normal. The spleen was not felt. Rectal examination was negative except for a grade two enlargement of the prostate.

The patient was not particularly anxious to submit himself to biliary drainage unless you insisted upon it. He had a rather complete study of hepatic function and certain other routine laboratory studies which might possibly have some bearing on the function of the liver. They are tabulated below.

Blood count	erythrocytes	4,770,000
	hemoglobin	13.5 grams
	leukocytes	9,600
	neutrophils	63 percent
	lymphocytes	33 percent
	monocytes	4 percent
Fasting blood sugar	93 mg.	
Blood Wassermann	negative	
Sedimentation	2 mm. (Westergren 1 hour)	

Urinalysis two specimens	both acid in reaction
	specific gravity 1.018 and 1.022
	chemical and microscopic examinations negative

Liver function tests	
Bromsulphalein (2 milligram dose)	no retention at the end of 30 minutes
No pathological urobilinogenuria	(two specimens)
Cephalin cholesterol flocculation	negative at 24 and 48 hours
Thymol turbidity	negative
Thymol flocculation	negative
Colloidal gold	negative
Serum bilirubin concentration	0.5 mg.
Alkaline phosphatase	0.5 Bodansky units
Prothrombin concentration	14 seconds or 95 percent
Total plasma proteins	6.24 grams percent
plasma albumin	3.39 grams percent
globulin	2.85 grams percent

In summary, I think it is safe to conclude there is no active parenchymatous change in the liver and no indication of chronic hepatic disease. The serum bilirubin concentration is at the upper limit of our normal, and there may be a slight depression in the plasma albumin fraction but this could be purely on a nutritional basis.

Sincerely yours,

(Signed) H. L. Bockus, M. D.

HLB:pm

SUMMARY

Criticism may be expressed as to whether this patient had cirrhosis of the liver. Although four doctors considered this patient's liver to be cirrhotic when viewed at the operating table, there was no biopsy to prove it. Removal of liver tissue for microscopy generally was not considered to be a safe procedure 25 years ago. Liver function tests of value had not then been developed.

Nevertheless, this case is considered worthy of report, particularly because of its long time follow-up.

Four agencies contributed toward this patient's clinical recovery.

A well regulated outdoor life in a warm climate.

During the early and mid-years of his recovery his liver was protected by a high carbohydrate, relatively low protein and fat diet. In later years the protein was substantially increased with tolerance.

Removal of bile from his stomach best relieved nausea; gastric lavage and periodic biliary drainage were helpful. The intensive liver drainage in 1924 got him off to a good start.

Lastly, antispasmodic—sedative—hepatic medication, with good intestinal elimination was important.

A comparison of tests, made in 1927 and in 1933

showed substantial improvement in liver function as a result of treatment.

Clinical recovery of this patient can be claimed in 1946, attested by the steady symptomatic improvement

of Mr. X., by substantial weight gain, by tolerance of a normal diet, and by satisfactory results of liver function tests as conducted by Dr. Bockus.

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Diabetes Mellitus, Fibrocongestive Splenomegaly (Banti's Syndrome) and Infectious Mononucleosis.

By

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THIS CASE is considered worthy of reporting for several reasons. Search of the recent literature has failed to reveal any such report of the concurrence of diabetes and Banti's syndrome. The first observers of this patient concluded he had a lipoid disease because of the diabetes and peculiar eye findings. Marble et al(6) reported that of 60 children with hepatomegaly, 31 had splenomegaly. There is no mention by Joslin(4) of such a complication as found in our case; and Root(8) agrees with its rarity. The results of surgery and its effect on the patient's diabetic status are noted. A late complication of infectious mononucleosis added further interest to this case. A two-year follow-up is appended.

D. D. L., a 20-year-old private, was born in 1923 in Iowa where he lived on a farm all his life. His past medical history was negative except for measles, pertussis, varicella, and scarlet fever in early childhood. His father and only brother are living and well. His mother died at the age of 50 from diabetes.

He entered the army on February 25, 1943. He was at various camps in California, Florida and Virginia and was well until October 24, 1943 in Virginia. There he developed an acute upper respiratory infection, and because of the cough, productive of mucopurulent sputum and nose bleeds, he reported on sick call on November 1, 1943. During the course of the physical

examination, an abdominal mass was palpated and led to his admission to a station hospital the same day.

No further significant history was obtained except that he recalled one previous nose bleed in May, 1943. Review by systems was negative. He had noted no weight loss, stating that he weighed about 160 pounds on entering the army.

Physical examination revealed the following significant findings. His weight was 135 lbs. There were small petechial spots over both ankles and an ecchymotic area near the right knee. There was slight pitting edema over both tibiae. The abdomen appeared full in the upper half. A firm, rounded mass was palpated in the left upper quadrant of the abdomen extending to the midline and about 2 cm. above the umbilicus. The liver edge was not palpable.

Routine urinalysis revealed a 4 plus sugar. Fasting blood sugar was 260 mg. on November 3, with persistent glycosuria and some acetoneuria. A diabetic diet was ordered and the patient was started on insulin. He received from 40 to 70 units of insulin daily with improvement in blood sugar, although he continued to have marked glycosuria. (Fig. 1). All other laboratory tests were within normal limits except for persistent leucopenia (Tables 1 and 2).

X-ray revealed the following: chest was negative, except for a congenital anomaly of first right rib. The skull, knees and pelvis were negative. The abdomen

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Submitted Dec. 11, 1946

TABLE I

	11-3	11-24	11-26	11-29	12-9	12-14	12-18	12-30	1-13	1-17	1-24	2-2	2-3	2-11	2-24
Hemoglobin (gm) -----	90%	95%	90%	100%	12.8	14.8	13.5	12.8	13.9	12.8	12		13.1	12.8	
R. B. C. (millions) -----	5.10	5.17	4.14	4.78	4.35	5.00	5.55	4.61	4.90	4.81	3.76	3.84	3.61	3.65	2.10
W. B. C. (thousands) -----	5.3	4.75	3.95	3.6	5.3		6.4	5.5	3.6	3.95	6.1	7.25	3.1	4.9	
Neutrophils (%) -----	61	56	51	64	53		61	67	58	69	72	72	65	64	
Lymphocytes (%) -----	27	39	39	22	46		33	30	38	26	24	28	30	32	
Reticulocytes (%) -----	0.8														
Thrombocytes (thousands) -----	193				80	120		100	110	95	35	100		65	125
Clotting time (minutes) -----					5	5½			4½	5½		4	4½	4½	
Bleeding time (minutes) -----					3	4			2	4		3½	3½	3	
Clot retraction time (hours) -----															
Sedimentation rate (mm) -----						9									
RBC fragility test (%) -----	0.42					0.40							0.44		
	0.34					0.34							0.34		
Smear for malaria -----					neg.										
Serology-Kahn -----	neg.				neg.										

TABLE I (Cont.)

	2-25	2-28	3-1	3-3	3-6	3-17	3-26	4-3	4-5	4-7	4-10	4-11	4-15	4-24
Hemoglobin (gm) -----	12.8	13.6		13.6	12.8	14.6	14.8	13.6	13.8			14.4		12.8
R. B. C. (millions) -----	4.10	4.45	3.40	4.05	3.95	3.90	4.05	4.70	4.37			5.06		5.18
W. B. C. (thousands) -----	18.1	11.8		15.5	8.00	6.9	7.15	6.8	6.0	6.5	15.0	31.2	49.3	18.2*
Neutrophils (%) -----	87	67		62	75	70	61	47	40	51	27	14	7	8
Lymphocytes (%) -----	10	18		35	16	19	32	50	53	47	73	86	93	88
Reticulocytes (%) -----														
Thrombocytes (thousands) -----	225	500	1000	2500	400	2160	240		250					450
Clotting time (minutes) -----						4½								
Bleeding time (minutes) -----						2½								

TABLE II

	11-3	11-13	11-24	12-14	12-22	1-4	1-13	1-15	1-24	1-31	2-7	2-14	2-28	3-14
Urea Nitrogen (mg) -----	8.5	8.5		13										
Total serum protein (gm) -----				6.97						6.5	6.50			
Serum albumin (gm) -----											4.24			
Serum globulin (gm) -----											2.26			
Blood cholesterol (mg) -----		189	196	317	264	172	218			232	222			204
Cholesterol esters (mg) -----				207	132		163			169	144			165
Icterus Index (units) -----	9.7	10	12	10		7.5							7.5	
Urobilinogen -----			1-20	1-40			norm.							
Bromsulphalein test -----								30% 35 min.				30 min. 40%		
Phosphatase-alkaline (units) -----									10.45					
Phosphatase-acid (Bod units) -----									0.40					
Hippuric acid test (gm) -----									3.18					
Cephalin flocculation test -----				neg.										
Prothrombin time (sec) -----										35 (25)				
Van den Bergh (bilirubin)														
Direct -----	neg.	neg.											0.52	
Van den Bergh														
Indirect -----	3.5	1.8											0.96	
	4-7	4-15	4-24	4-28										
Heterophile antibody—complete—	1-64	1-128	1-32	1-128										
—partial—	1-512	1-512	1-128	1-512										

showed a grossly enlarged spleen with the lower level at the fourth lumbar vertebra. The kidneys were normal in size and shape, with the left kidney slightly lower in position.

On November 15, 1943, the ophthalmologist reported as follows: "Definite scleral icterus. On each side of the cornea is a small wedge shaped yellowish deposit of fat-like tissue resembling pinguecula. Fundi show

prominent arterioles. Maculae show some colloid deposition. The arteries show an increase in the high-lights. The patient is undoubtedly one of the lipid histiocytic dystrophies. Xanthomatosis between Gaucher's and Hand-Schuller-Christian disease must be considered. Advise biopsy of mass on the eye".

On November 27, 1943, a biopsy of the conjunctiva was done. This showed only fatty tissue. Another

eye examination on November 30 reported "Subconjunctival hemorrhage absorbing. Slit lamp shows yellowish (canary) deposition of solid substance along the vessels. It resembles "egg" drops. No corneal changes are seen".

In December, 1943, the patient was admitted to our service at Walter Reed General Hospital with a diagnosis of diabetes mellitus and splenomegaly, with probable lipid disease.

The patient was asymptomatic. He denied having symptoms of diabetes at any time. He had not noted any weight loss nor increase in fullness of the abdomen. He stated that his abdomen had not been examined at the time of his induction into the army in February, 1943. Nor had he noted the yellowish deposits on his eyes. Although his mother had diabetes, he did not know the exact cause of her death.

revision of the Binet-Simon test showed him to be of borderline intelligence with the mental age of 10½ years.

An intravenous pyelogram was normal. X-ray of the esophagus failed to reveal any varices. A gastrointestinal series showed displacement of the stomach, small intestine and splenic flexure of the colon by a mass in the left upper quadrant of the abdomen.

On admission, the patient was placed on a maintenance diet of Carbohydrate 220, Protein 65, and Fat 90. With this he was given Protamine Insulin 50 units plus regular insulin 10 units. The glycosuria cleared almost completely but he showed a persistent hyperglycemia, as high as 280 mg. on several occasions. The insulin was gradually reduced so that by February 13 he was getting 40 units of protamine insulin daily. (Fig. 1).

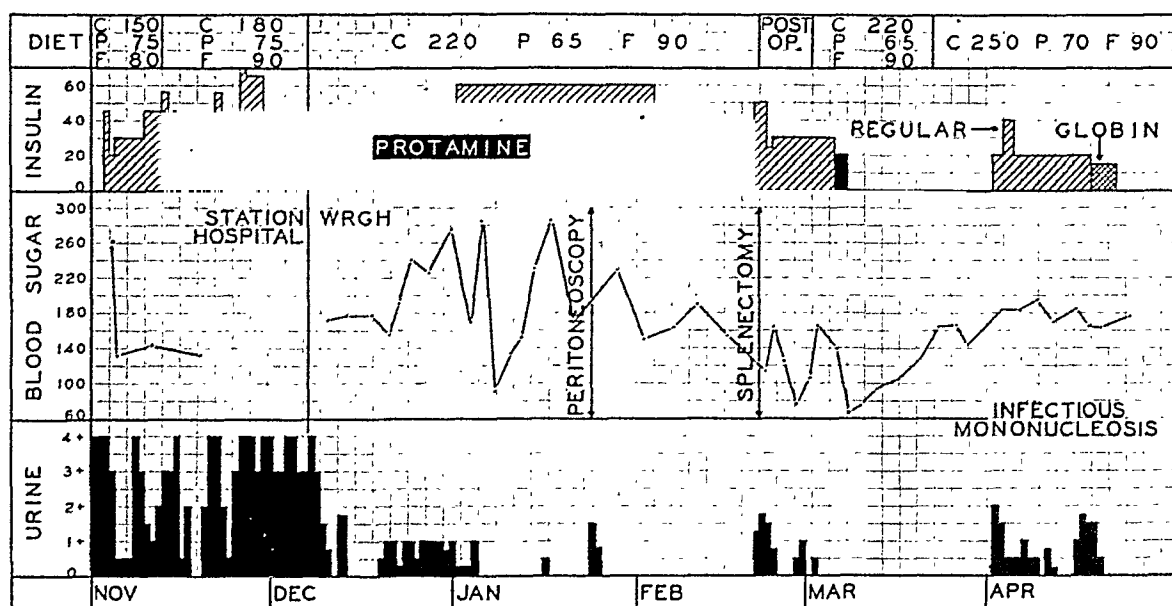


Fig. 1

Although the patient seemed alert, it was readily apparent that he was not very intelligent. He did not comprehend questions too well and there was a marked slurring of his speech with stuttering at times.

Physical examination revealed the following significant findings: weight 141 lbs., congested right eye, brownish areas of pigmentation over both ankles and marked enlargement of the spleen. (Fig. 2).

On December 9, the ophthalmologist reported "Congestion of right bulbar conjunctiva from recent removal of pterygium. Small petechial subconjunctival hemorrhages. Slit lamp examination negative. Normal optic discs, vessels and maculae. No hemorrhages or exudates."

On December 18, the neuropsychiatrist found a rather dull indifferent individual who graduated from the eighth grade at the age of 15. He was never very bright and now shows considerable psychomotor retardation. The patient has always had a mild hesitation in his speech which develops into a marked stutter whenever he is under emotional stress. The Stanford

The cause of the splenomegaly was investigated from several angles. Sternal marrow was obtained by aspiration on December 18, and was reported within normal limits, no Gaucher cells being found (Table 3). Biopsy of the pigmented skin about the left ankle was done on January 5, 1944. This was reported by the pathologist (W. S. Randall) as showing no abnormal pigmentation in the corium and no inflammatory reaction.

On January 24 peritoneoscopy was done (J. E. Hamilton). The spleen was found to be of normal size and color, but much enlarged. The liver was normal in size and color with a somewhat uneven surface. Biopsies were taken from the liver and spleen with minimal hemorrhage. On histologic examination the hepatic cells showed nothing of significance, generally being in a glycogen storage phase. (Fig. 3). The spleen showed a thickened capsule. The pulp showed no follicles, moderate fibrosis and quite prominent sinuses. (Fig. 4).

All laboratory findings were within normal limits (Tables 1 and 2), except for moderate anemia (Micro-

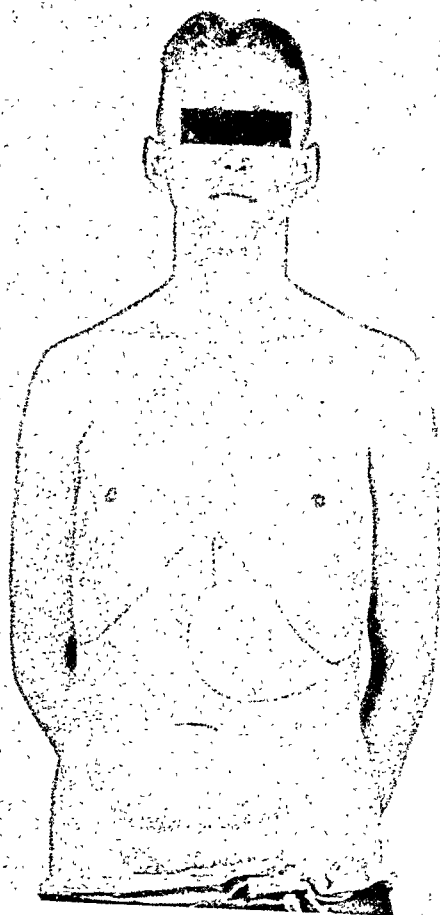


Fig. 2

TABLE III

BONE MARROW

Hematocrit: Fat	2 %	
Buffy	3.5 %	
Packed RBC	43.5 %	
Serum	51.0 %	
Differential:	D.D.L.	Normal Average
Myeloblasts	1.6	2.0
Promyelocytes	1.6	5.0
Myelocytes	14.4	13.8
Metamyelocytes	17.2	22.0
Neutrophils	12.8	20.0
Eosinophiles	2.8	2.0
Basophiles	0.5	0.2
Lymphocytes	10.8	10.0
Monocytes	1.2	2.0
Plasma cells	0.0	0.4
Reticulum cells	1.6	0.2
Total	64.8	77.6
Megakaryocytes	0.0	0.4
Pronormoblasts	5.2	4.0
Normoblasts	30.0	18.0
Total	35.2	22.4
Myeloid-Erythroid Ratio:	1.84:1	3.46:1

cytic hypochromic), leucopenia, thrombocytopenia, hypercholesterolemia, bromsulphalein retention and slightly increased prothrombin time.

On February 22, 1944, a splenectomy was done (J. E.

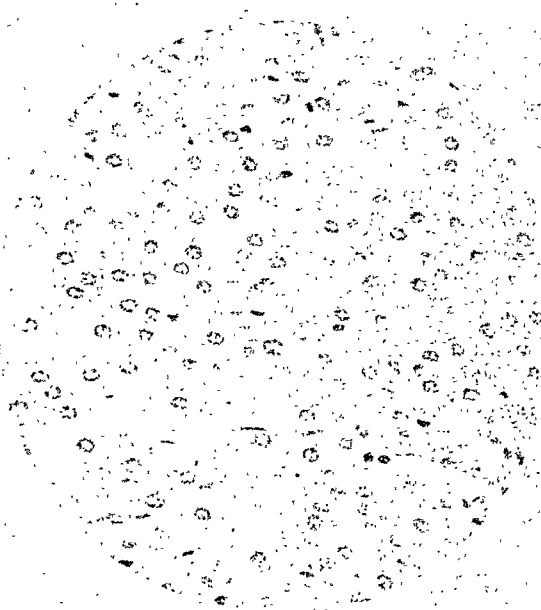


Fig. 3

Hamilton) under continuous spinal anesthesia. The operation report was as follows: "The spleen was found to be enormously enlarged, extending from high under the diaphragm to the level of the umbilicus. There was an accessory spleen in the lower pole and one in

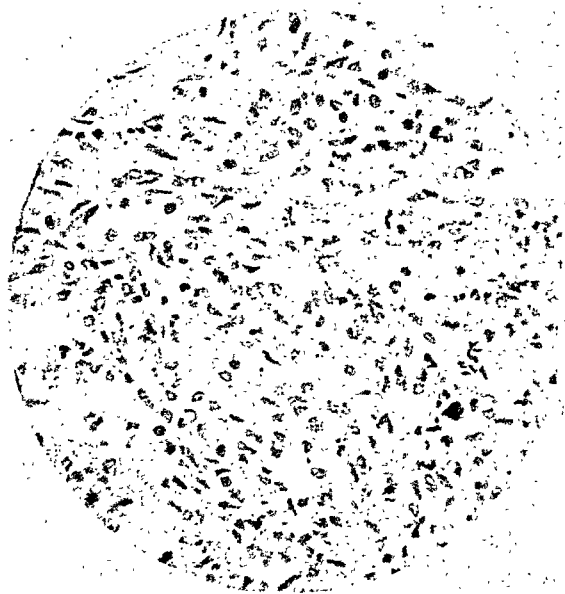


Fig. 4

the hilus. The liver appeared normal. There were no adhesions between the spleen and the diaphragm. The splenic artery was first isolated and ligated and divided in the region of the tail of the pancreas. This caused a moderate shrinkage in the size of the organ. One-quarter cc. of adrenalin was injected into the spleen causing a slight further shrinkage and raising the blood

pressure to 210 systolic. The spleen was too large to deliver on the abdominal wall and therefore the pedicle was ligated in multiple fashion, catching the vasa brevia first and then the posterior portion of the pedicle. There was moderate hemorrhage, both from several small bleeders that escaped in the pedicle and also some bleed-

maintenance diet, three-fourths of the diet from February 27, and his full diet beginning on March 1. He received 15 units of regular insulin daily from February 25 to March 6, and then 20 units of Protamine on March 7 and 8. Thereafter he required no further insulin. (Fig. 1). At no time following this immediate post-operative period did he have a fasting blood sugar over 165 mg.

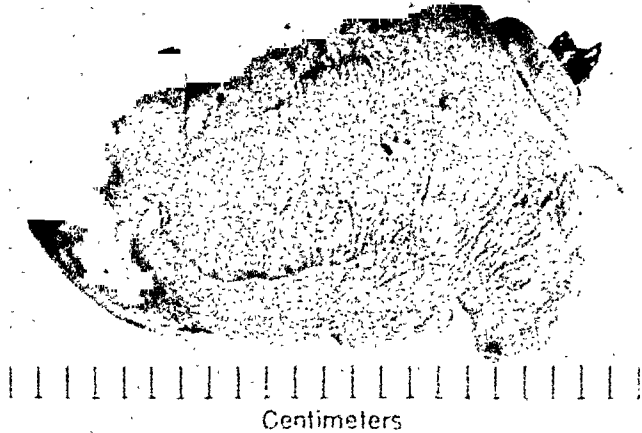


Fig. 5

ing from the pedicle itself. Patient left the operating room in good condition".

From February 22 to 24 inclusive, the patient was treated with intravenous amigen and 5% glucose, the latter being covered with regular insulin, one unit for each 2 gm. of glucose, and with 500 cc. whole blood transfusions daily. On February 23, he had a sudden

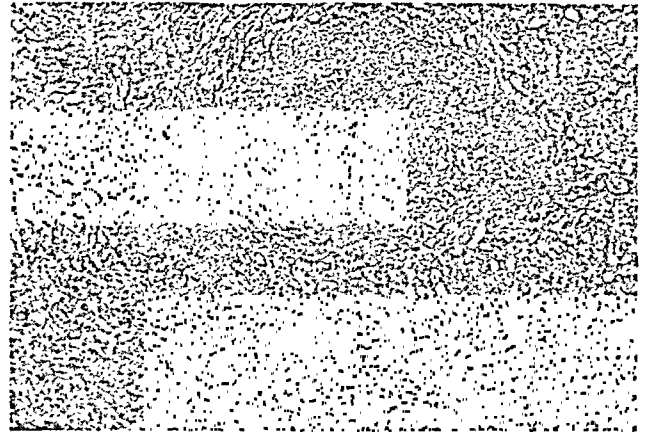


Fig. 7

The pathological report on the spleen was as follows: "Gross (Figs. 5 & 6) — Spleen weighing 800 grams, measuring 17 by 10-14 by 2-4 cm. There is a 2 cm. accessory spleen attached at the hilus. The outer surface is smooth and the capsule is slightly thickened. The cut surface is homogeneous without any remaining normal follicles. The trabeculae are rather prominent." "Microscopic (Figs. 7 & 8) — The capsule is moderately thickened and everywhere intact. The architecture of the spleen is somewhat distorted, there being

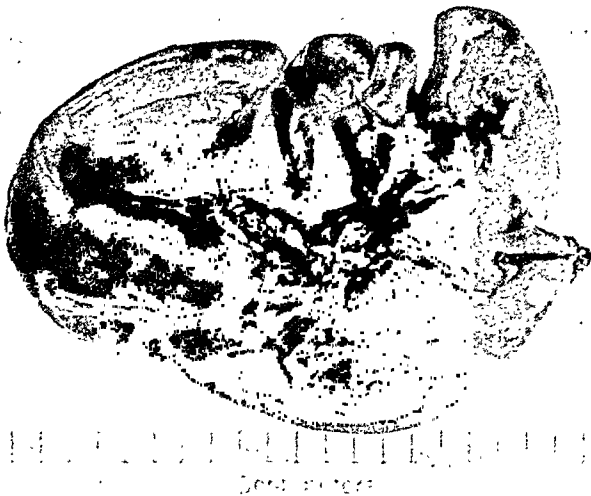


Fig. 6

massive collapse of the right lung. A nasopharyngeal catheter was inserted far enough to aspirate some plugs of mucus from the tracheo-bronchial tree. Within an hour, X-ray showed the lung to be almost completely re-expanded. He had some elevation of temperature to 103, from February 22 to 28 inclusive. Sulfadiazine was administered from February 20-29 inclusive.

Beginning on February 25, he was given half his

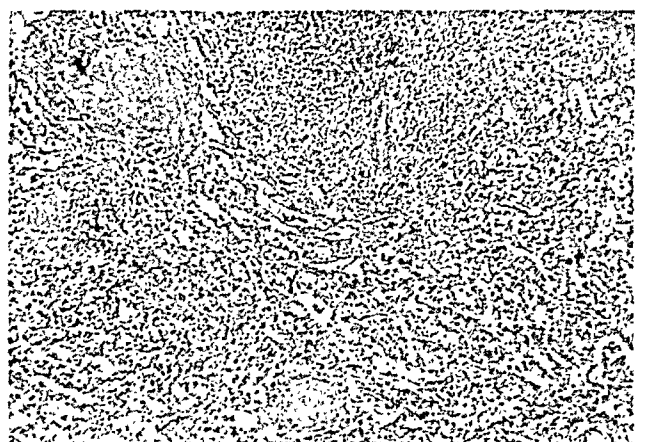


Fig. 8

only a few remaining compressed atrophic follicles. The sinuses are widely dilated and contain a small amount of blood. There is thickening of the walls of these structures and everywhere there is moderate fibrosis. There is no apparent proliferation of the endothelial lining of the sinus structures. Sections through the accessory spleen show a moderately thickened capsule and while the pulp is somewhat more normal than the

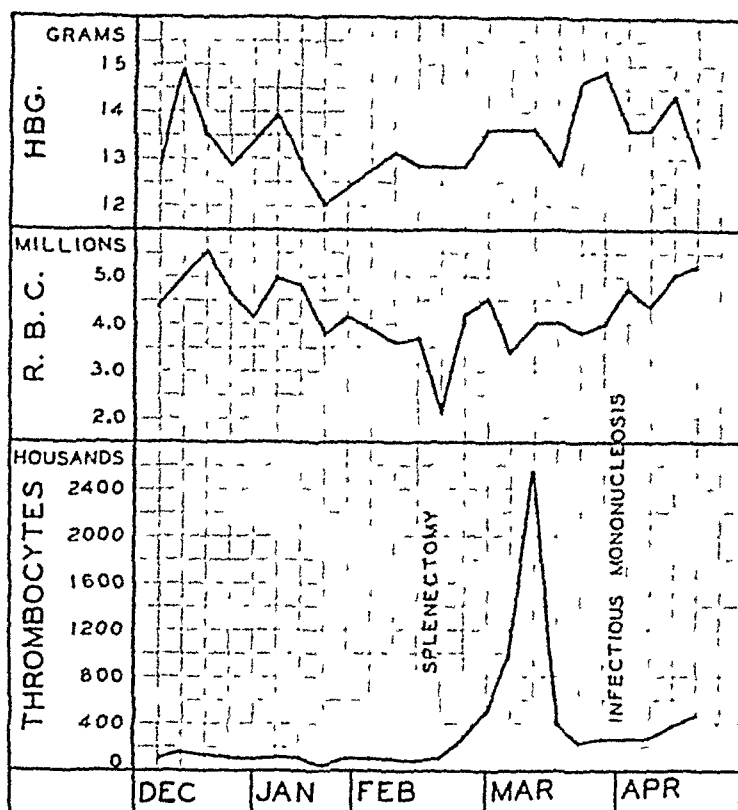


Fig. 9

large spleen, here there is some follicular atrophy and dilatation of the sinuses but fibrosis is not yet pronounced."

"Diagnosis: Chronic congestive splenomegaly, compatible with Banti's Syndrome."

Insofar as his blood counts were concerned, he showed a rather abrupt rise in thrombocytes to a maximum of 2,160,000 on March 3 (Fig. 9) and later a return to a normal level. His leukocyte count, which had reached 18,000 immediately post-operatively returned to a level of 6-8,000 (Fig. 10), which was well above the pre-operative range.

On March 21, after twelve days without insulin, a glucose tolerance test after 100 gm. of glucose showed a diabetic curve with a peak blood sugar at 2 hrs. of 364 mg. (Fig. 11). His diet was increased to Carbohydrate 250, Protein 90, and Fat 100, calories 2380 and the patient was ready for discharge. The abdominal incision had healed well without incident.

On April 1, the day prior to his scheduled discharge the patient developed a severe headache with marked malaise. The headache failed to respond to any of the analgesics. By the following day he had a marked fever up to 102.4 degrees. Physical examination was negative. X-ray of the chest on April 4 and April 7 was negative. Administration of sulfadiazine had no effect on his fever. Blood counts were within normal limits for the first week except for a slight relative lymphocytosis. This plus the presence of a morbilliform rash

over the palate and buccal mucous membrane which appeared later, led to a diagnostic impression of infectious mononucleosis. A heterophile antibody (Paul-Bunnell) test was taken on April 7. On April 9, lumbar puncture showed normal cerebrospinal pressure. There were no cells, and the chemistry was normal.

On April 10, he had a leukocytosis of 15,000 with a reported differential of 73% lymphocytes (Fig. 10). A special smear the same day showed these cells to be chiefly Rieder cells. The heterophile antibody test taken on April 7 was finally reported as complete 1-64 and partial 1-512, confirming the diagnosis of infectious mononucleosis. The patient continued to have fever for two weeks. His white count rose to a peak of 49,000 with 88% lymphocytes (Fig. 10). He continued to have headache during the entire two weeks of fever. Further heterophile antibody tests showed more complete agglutination. (Table 2). The patient left the hospital for his home on April 28, afebrile but still showing lymphocytosis.

He continued on his diet alone until September, 1944, when he had some glycosuria and was placed on 20 units of protamine insulin daily by his family physician. He remained on this dose until November, 1945, when he was hospitalized for a check-up by the Veterans' Administration. He was found to require Protamine 32 units plus regular insulin 8 units for complete diabetic control. When last heard from, in May, 1946, he was still on this insulin dose and feeling very well.

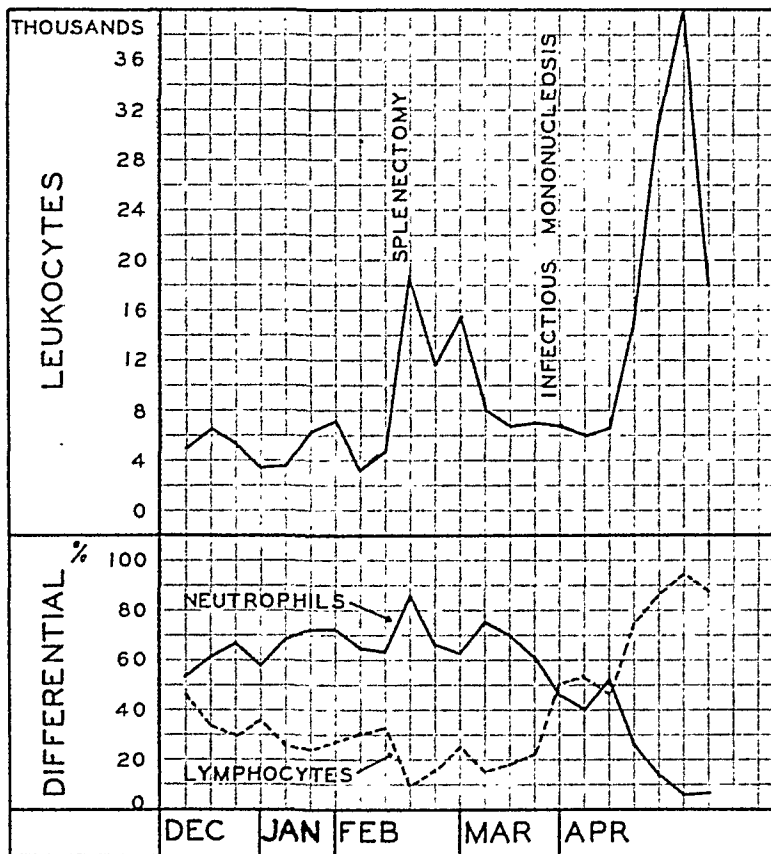


Fig. 10

DISCUSSION

In the differential diagnosis various known causes of splenomegaly (10) were considered and eliminated.

In view of the transfer diagnosis of lipid disease, the persistent hypercholesterolemia and the removal of a lipid corneal deposit at the first hospital, various forms of xanthomatose involving the spleen were considered, as outlined by Dreyfuss and Fishberg. (2). Such a case was also reported by Herbert (3). The absence of skin xanthoma, the normal bone marrow smear and the absence of lipid in the spleen by peritoneoscopy-biopsy eliminated Gaucher's disease, diabetic lipemia, and localized xanthoma of the spleen as causes for his splenomegaly. Joslin (4) has reported lipid corneal deposits in diabetics with hypercholesterolemia. The patient's hyperlipemia was attributed to his diabetes, since the cholesterol esters were within normal limits and the total blood cholesterol became normal after his diabetic state was controlled (9).

Hemochromatosis had to be considered in view of the fact that pigmentation of the skin may be absent in 20% of the cases. However, hemochromatosis has never been reported under the age of 25 years and is most frequent in middle age. The negative skin biopsy further added to our clinical impression that this patient did not have hemochromatosis.

Syphilis, tuberculosis, sarcoidosis, parasites, lymphoma and leukemia were readily eliminated by study of the bone marrow and the peripheral blood, the absence of fever and the peritoneoscopy-biopsy of the spleen and the fact that the patient had never been out of the United States.

Thrombocytopenic purpura was ruled out because of the absence of bleeding tendency under our observation, normal red cell fragility, normal icterus index, negative tourniquet test and normal clot retraction.

The syndrome of primary splenic neutropenia (1) was considered but discarded in view of the normal neutrophile count and normal bone marrow.

The diagnosis of chronic congestive splenomegaly (splenic anemia, Banti's disease) was thus clearly established. The clinical picture was that of a young man, with a disease of insidious onset, an enlarged spleen, two episodes of epistaxis, moderate anemia, persistent leucopenia with normal differential and thrombocytopenia. There was some evidence of liver damage in retention of bromsulphalein on two tests.

The sternal marrow differential was reported as normal, but there was a myeloid-erythroid ratio of 1.84:1 compared with a normal of 2.75:1 or higher. Limarzi et al (5) have reported that early in Banti's there is a myeloid hyperplasia. They believe that the condition of the marrow may be of prognostic significance for splenectomy, that erythroblastic marrow with reversal of the myeloid-erythroid ratio points to a poor result from the splenectomy. In their 21 cases, the M-E ratio was 1.22 to 1. Doan (1) believes that the earlier in the disease the spleen is removed, the safer and better. Others, quoted by Wintrobe (10), agree to splenectomy but believe a more careful selection of cases is necessary to avoid fatalities, early or late.

The pathogenesis of congestive splenomegaly is still a moot question. Portal hypertension due to obstruction of the portal or splenic vein has been reported in many instances. But its absence in other cases has led

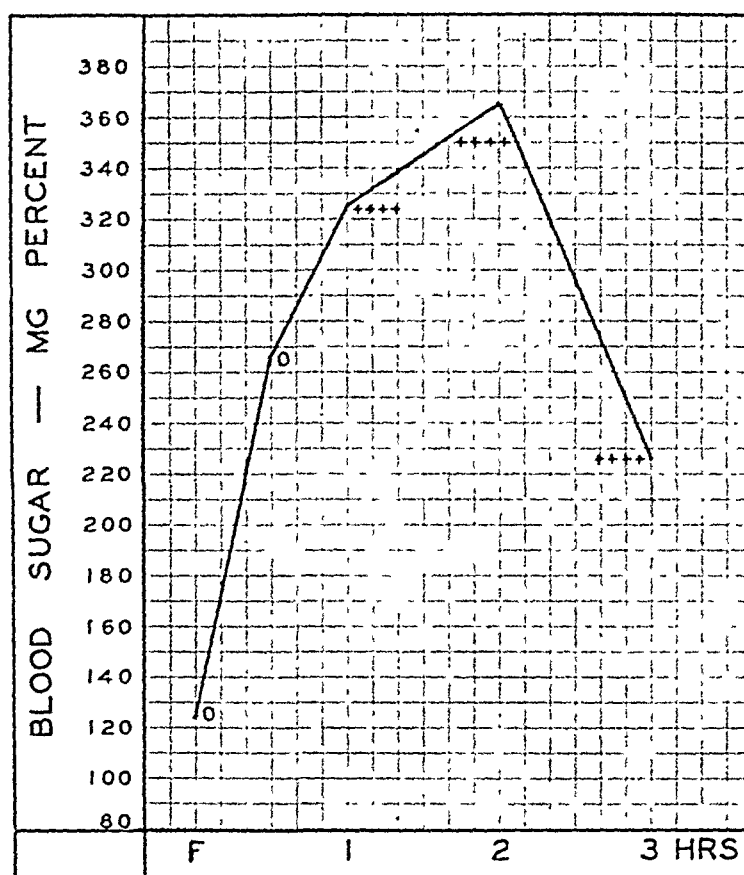


Fig 11

Ravenna (7) to postulate that the disease is primary in the spleen and is due to toxic, infectious or parasitic damage to the spleen parenchyma itself, which is accompanied by fibrosis. The changes are primarily due to the lesions of the splenic arterioles which fail to control the inflow of blood. The consequent congestive splenomegaly causes disturbances in the portal blood flow and leads to cirrhosis of the liver and venous thrombosis.

In our case, at operation, no attempt was made to measure the pressure in the splenic vein. The surgeon could find no evidence of obstruction in the portal system within the field of his operation. The rapid improvement in the patient's diabetic state is inexplica-

ble. If one agrees with the toxic theory of a primary splenic disease, then perhaps removal of this factor may account for the prompt improvement in the patient's carbohydrate tolerance. Then again, if the portal hypertension existed and was relieved by the splenectomy perhaps that would also account for the improvement in the patient's diabetes by improving the circulation to the pancreas. Such an abrupt improvement post-operatively in diabetes must be exceedingly rare. The usual picture after most operations is a depreciation in tolerance, a tendency to ketosis and an increased need for insulin. Our patient behaved as though some source of infection had been removed by the splenectomy.

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A Soluble Phenolphthalein Laxative

By

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THE CATHARTIC effect of phenolphthalein was first noted by v. Vamossy in 1900, and it was during the ten years subsequent to his observation that most of the clinical investigations were conducted. Opinion differs as to its mode of action. Vamossy and also Tunnicliffe, in 1902, attributed the action of the drug to high osmotic pressure produced thus: in the acid medium of the stomach, phenolphthalein remains unchanged but upon reaching the alkaline intestine it is converted to the more soluble, and hence more active, sodium salt, the diffusive powers of the salt increasing osmotic pressure. The proponents of this explanation point out the correlation of the more marked effect of phenolphthalein in man than in animals with the greater alkalinity of man's intestinal tract. Caldwell and Crane, in 1929, put forth the theory that phenolphthalein is dissolved in the bowel by bile and alkali and develops a mild irritant action on both the small and large intestine, more definitely on the latter. Ott and Scott, in 1908, reported experiments in which the drug acted directly on excised intestinal muscle, and Alexandrine was quoted by Caldwell as claiming that phenolphthalein stimulated peristalsis of the ileum and cecum. Roentgenographic studies by Caldwell, however, showed no local effect on the movements of the stomach and small intestine.

There is substantial evidence that the drug may be absorbed into the blood from the large intestine, carried to the liver, secreted into the bile and intestine and reabsorbed into the blood again, thus accounting for the fact that its mild aperient action lasts for several days, before the drug is gradually eliminated in the feces and urine.

The few recorded cases of toxic effect are in doubt, and very large doses have been given to man (several grams orally and one-half gram subcutaneously) without untoward effect. Phenolphthalein itself does not produce local irritation but its soluble salts are extremely irritating. Apparently it is not readily absorbed, as is demonstrated by the large amounts found

in the feces (up to 85%), and only following large doses can it be detected in the urine.

Investigations into the possibility of developing the solubilized derivative described in this report were initiated in 1933. Preliminary work established that neither phenolphthalein nor its sodium salt could qualify on the score of solubility and palatability. Both are bitter in solution, at least 50% alcohol being required for the dissolution of phenolphthalein, and the sodium salt is subject to rapid decomposition in solution.

Examination of the literature indicated that the naturally occurring laxative principles of cathartics were water soluble glucosides of the hydroxyanthraquinone group, further, that it was the beta type of glucoside that released active drugs by enzymatic action. Thus synthesis of the beta glucoside suggested itself and was accomplished in 1934 by the reaction of phenolphthalein with acetobromoglucose in the presence of silver oxide and quinoline, according to the process described in U. S. Patent 2,216,734.

The derivative is almost infinitely water soluble, alcohol soluble, odorless, colorless, nearly tasteless, stable in liquid or solid form, yet capable of being hydrolyzed in the digestive tract.

The preparation for oral administration is a palatable elixir consisting of true fruit raspberry flavor, 9% alcohol, 38% sugar, and 1.62% of phenolphthalein beta diglucoside, with small amounts of supplementary flavoring, compounded to supply 1 grain per teaspoonful of the laxative principle (equivalent to 0.237 grain of combined phenolphthalein). Rigid stability tests have demonstrated no alteration of the active ingredient on aging.

TOXICOLOGICAL STUDIES

Preliminary toxicity investigations failed to reveal a lethal dose. By intraperitoneal injection of 10% aqueous phenolphthalein beta diglucoside in four white rats, a tolerated dose of 2.17 gms./Kg. was established—the equivalent of a 152 gm. dose for a man of 154 pounds. Analysis of the feces demonstrated that the drug had been split in the digestive tract to yield free phenolphthalein. On this basis extensive animal testing prior to work with human subjects, seemed justified.

Before proceeding with further work on toxicity preparatory to clinical testing, it was felt desirable to evaluate the reported incidence of sensitivity to phen-

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olphthalein. A thorough literature survey was made, and in addition, first-hand information was obtained from leading dermatologists as to the importance of published statements on allergic reactions to phenolphthalein. As a result of this study it was concluded that phenolphthalein is a safe and acceptable laxative

and that the occurrence of allergic reactions is extremely rare in view of the millions of doses consumed annually. The cases cited seemed to indicate that the few individuals who do react to phenolphthalein may be desensitized, that most reactions appear after the drug has been taken, consciously or unconsciously, for some

CHART NO. I
TOXICITY TESTING OF PHENOLPHTHALEIN BETA DIGLUCOSIDE
A (Feb. - April, 1938) (using rats) B (Feb. - May, 1945)

Rat	Sex	Symptoms during study	Findings at autopsy	Dosage during study and method	Period of study	Rat	Sex	Symptoms during study	Findings of autopsy
A	m	none	acute bronchitis	2 mgm/Kg by stomach tube daily for	2 weeks	1	m	wt. loss of 35 gms.	all essential organs normal; obstruction by broken tube
B	m	none	acute bronchitis slight toxic nephrosis	"	"	2	m	none	all essential organs normal
C	m	none	bronchopneumonia kidney congestion	" CONTROL	"				
D	f	none	acute bronchitis; sl. toxic nephrosis & splenitis	2 mgm/Kg daily 4 mgm/Kg daily by stomach tube	2 weeks 2 weeks	3	m	diarrhea twice	all essential organs normal
E	f	diarrhea once	acute bronchitis; slight splenitis and nephrosis	"	"	4	m	diarrhea once	"
F	f	none	moderate toxic nephrosis	"	"	5	m	none	"
H	f	none	glomerulonephritis (chronic)	2 mgm/Kg daily 4 mgm/Kg daily 6 mgm/Kg daily	2 weeks 2 weeks 2 weeks	6	m	none	"
K	f	none	acute bronchitis	"	"	7	m	none	"
L	f	diarrhea once	toxic nephrosis	"	"	8	m	diarrhea once	"
(using rabbits)									
M	m	none	no findings	2 mgm/Kg daily by stomach tube	2 weeks	1	m	none	no findings
N	m	none	parasitic liver infestation	"	"	2	m	died 11th day	pulmonary edema no inflammation of stomach or intestines
O	m	none	parasitic liver infestation	"	"				
P	f	diarrhea once	acute colitis; toxic nephrosis	2 mgm/Kg daily 4 mgm/Kg daily by stomach tube	2 weeks 2 weeks	3	m	some diarrhea	no findings
S	f	none	no findings	"	"	4	m	none	no findings
T	f	none	acute enteritis	"	"				
W	m	none	no findings	2 mgm/Kg daily 4 mgm/Kg daily 6 mgm/Kg daily by stomach tube	2 weeks 2 weeks 2 weeks	5	m	none	no findings
X	m	none	no findings	"	"	6	m	none	no findings
Y	m	none	no findings	"	"				
R	m	diarrhea died 21st day	advanced post-mortem decomposition	2 mgm/Kg daily 4 mgm/Kg daily	2 weeks 1 week				
Z	m	none	no findings	6 mgm/Kg daily	3 weeks				

NOTE: Study A was carried out by Dr. Frederick F. Yonkman with the assistance of Dr. Charles F. Branch.
Study B was carried out by Dr. Walter L. Mendenhall with the assistance of Dr. Caroline tumSuden.

period of time. Hypersusceptible or specifically sensitized individuals have been reported to exhibit either excessive purgation or skin rashes. Fantus and his associates have shown that the drug is relatively non-toxic even in very large doses.

In this study 223 subjects received repeated doses of both phenolphthalein USP XI and phenolphthalein beta diglucoside, with no occurrence of skin reactions or other direct finding of sensitization to either drug.

A study of the toxicology and pathology of phenolphthalein beta diglucoside (using rats and rabbits), including certification of individual lots for use in clinical testing, was conducted by Dr. Frederick F. Yonkman in 1938; his findings were confirmed in every respect in 1945 by Dr. Walter L. Mendenhall (see Chart I). To preclude introducing variation in test material, the assignment of all samples for toxicity and clinical testing was the responsibility of one worker throughout the investigations, and careful records were kept of chemical analysis and toxicity tests on each sample.

A complete account of the toxicity tests is omitted since it would consist largely of an enumeration of results which confirmed the initial findings, which once established, were checked by independent investigators.

In the studies described in Chart I, autopsy revealed no morphological or histopathological changes attributable to phenolphthalein; when a study of residual urine was possible, there was no evidence of renal irritation. Any changes observed could be attributed for the most part to upper respiratory infections, then prevalent, as confirmed in control animals. Gradually increased dosage established a minimum lethal dose in the rabbit by vein of 5 gm./Kg., or the equivalent of three-quarters of a pound for a 154-pound man, administered in a single dose. Since the recommended dose for humans was intended to be 0.005 to 0.195 grams (1/12-3 grains) orally (and toxicity is less orally than intravenously), the wide margin of safety is obvious, and phenolphthalein beta diglucoside may be considered a safe and non-toxic drug.

The elixir vehicle without the phenolphthalein derivative, in comparison with the complete formulation, was tested in amounts up to 8 cc. daily by stomach tube in rabbits and rats and found to be non-toxic. Toxicity tests on the elixir were carried out on two occasions since a large number of accidental deaths in the first study demanded improvement in technique in administering the drug; repetition of the study permitted a maximum number of animals to survive the experimental period (see Chart II).

In certifying lots for clinical use, the routine procedure was to administer 1 gm./Kg. intravenously to rabbits and 4 mg./Kg. per os to rats.

Dr. Maurice Rosenthal, after repeating some of the animal studies to be assured of toxicity findings, made a comparative clinical examination of phenolphthalein and phenolphthalein beta diglucoside, taking as his sub-

jects five age groups. Having established effective dose ranges at all age levels, Dr. Rosenthal and Dr. Maurice Blatt, working independently, evaluated the finished elixir. A detailed account of the clinical work follows and is summarized in Chart III.

CLINICAL STUDIES

1½ - 5 Years Group. (Not hospitalized). Because of infrequent need of laxatives in this group of twenty-five institutionalized children, the observation period extended to six months before a sufficient number of doses had been given for adequate clinical evaluation. The four weeks prior to investigation served as a control period in all the clinical studies described in this report. The children in this group were free of chronic ailments and on the basis of intestinal physiology could be classified: 16, normal; 6, moderately constipated; and 3, chronically constipated. The diet was standard throughout investigation and control periods. Laxatives had previously been used only infrequently and irregularly. Administration of the drug under study was daily; the two drugs—the diglucoside and phenolphthalein USP—were alternated at bimonthly intervals; thus each subject served as his own control. The level of dosage was as follows (in grains):

	Diglucoside	USP Phenolphthalein
Total dosage during period of study	11 5/12	11 1/6
Total number of bowel movements	133	122
Actual dose per patient	1/12 - 1/6	1/12 - 1/8
AVERAGE EFFECTIVE DOSE	1/12	1/12

Untoward reactions were rare. Vomiting occurred once with the USP preparation although four similar doses were subsequently tolerated; cramps were complained of in two cases with both preparations; but here again, repeated doses of either were not associated with that complaint. It is significant to note that the period of administration of the drugs extended to six months and yet no skin reactions were observed. Urinalysis and blood studies failed to reveal any pathological changes due to either preparation. Phenolphthalein was not detectable in the urine; stool examination was negative.

It can be concluded from study of this group that the diglucoside was a little more than twice as effective as phenolphthalein on an equimolecular basis. As judged by elapsed time for evacuation, the more effective compound was also the diglucoside (14 hours as compared to 16-17 for phenolphthalein).

3 - 8 YEARS GROUP

(Hospitalized, bedridden). This group of twenty-six tuberculous children presented varying degrees of constipation; enemas and laxatives had been used frequently. Standard hospital diet was maintained throughout the experimental period of eight weeks as well as during the control period.

The subjects in this group were divided as follows:

CHART NO. II

TOXICITY TESTING OF PHENOLPHTHALEIN BETA DIGLYCOSIDE ELIXIR VEHICLE
(Administration per os)

Study during May - June, 1939

Rabbit	Sex	Dosage		
A1	m	14 doses of 4 cc. each		
		1 dose of 5 cc.		
		5 doses of 6 cc. each		
		1 dose of 5 cc.		
A2	f	17 doses of 4 cc. each		
		1 dose of 5 cc.		
		1 dose of 6 cc.		
		2 doses of 8 cc.		
A3	m	first animal	second animal	
		3 doses	15 doses	of 4 cc. each
			1 dose	of 5 cc each
		1 dose		of 6 cc each
		1 dose		of 8 cc. each

All animals were normal throughout course of study and autopsies were not performed. The first animal designated A3 "drowned", i. e.—the solution oozed up through the catheter, was drawn into trachea, thus interfering with respiration.

Study during June - July, 1940

Rabbit	Sex	Dosage	
OR-11	m	7 doses of 4 cc. each	10 doses of 5 cc. each
OR-12	m	7 doses of 4 cc. each	10 doses of 5 cc. each
OR-26	f	7 doses of 4 cc. each	10 doses of 5 cc. each

All autopsies negative.

Administration Intravenous

VA1	m	4 injections of 8 cc. each
VA2	f	4 injections of 8 cc. each

IV-13	m	5 injections of 8 cc. each
IV-24	f	8 injections of 8 cc. each
IV-25	f	11 injections of 8 cc. each

Both animals were normal throughout course of study and autopsies were not performed.

Rabbit IV-13 died and autopsy showed bronchopneumonia; the other two animals were normal throughout study.

TOXICITY TESTING OF COMPLETE ELIXIR FORMULATION

(Administration per os)

Study during May - June, 1939

Rabbit	Sex	Dosage	Autopsy
B1	f	14 doses of 4 cc. each 1 dose of 6 cc.	rupture of lung by catheter
DIED final day of experiment			
B2	m	THREE animals used	
(1)		2 doses of 4 cc. each 1 dose of 6 cc.	"drowned"
(2)		1 dose of 4 cc. 3 doses of 8 cc. each	"drowned"
(3)		12 doses of 4 cc. each 3 doses of 5 cc. each	negative
B3	m	THREE animals used	
(1)		5 doses of 4 cc. each 1 dose of 6 cc. 2 doses of 8 cc.	"drowned"
(2)		4 doses of 4 cc. each	pneumonia
(3)		8 doses of 4 cc. each	negative

Study during June - July, 1940.

Rabbit	Sex	Dosage	Autopsy
OR-1	m	7 doses of 4 cc. each	negative
OR-2	m	10 doses of 5 cc. each	
OR-4	m		
OR-5	m		
OR-14	f		
OR-17	f		
OR-3	m	7 doses of 4 cc. each 5 doses of 5 cc. each 1 dose of 6 cc.	multiple liver abscesses; lung congestion.
DIED			
TWO animals used			
OR-15	f	(1) 3 doses of 4 cc. each (2) 3 doses of 4 cc. each 15 doses of 5 cc. each	"drowned" negative
TWO animals used			
OR-16	f	(1) 7 doses of 4 cc. each (2) 15 doses of 5 cc. each	bronchopneumonia negative
TWO animals used			
OR-18	f	(1) 7 doses of 4 cc. each (2) 15 doses of 5 cc. each	bronchopneumonia negative

(Intravenous administration)

VB1	f	3 injections of 8 cc.	lymphadenitis due to parasitic infection	Ten animals, five of each sex, each received 8 injections of 8 cc. each at 3-4 day intervals and were normal throughout the study.
VB2	m	4 injections of 8 cc.	negative	

The ten children in Group A were given 1/8 grain of phenolphthalein USP daily, for two weeks, followed by two weeks' medication of 1/12 grain of the diglucoside. The sixteen children in Group B received 1/8 grain of the diglucoside for two weeks, followed by two weeks' medication of 1/8 grain of the USP drug. The variation in initial dosage of the diglucoside was an attempt to judge the limitation of the drug's potency; it was established that equivalent effects were produced by the smaller amount.

In this group, dosage was increased daily in order to demonstrate development of tolerance to either drug. Initially no clinical manifestations were observed, and though later some subjects displayed intolerance to either drug, its resumption at the same or higher levels failed to produce symptoms. Acquired sensitivity was never seen. The level of dosage in grains was as follows:

	Diglucoside	USP Phenolphthalein
Total dosage during period of study	111.96	162.11
Total number of bowel movements	1023	802
Actual dose per patient	1/12 - 1/4+	1/8 - 1/2
AVERAGE EFFECTIVE DOSE	1/12	1/12

Urinalysis revealed no pathological changes except high concentration of the urine (frequently associated however with the febrile episodes of tuberculosis). Phenolphthalein was detectable in the urine only after doses of 1/2 grain of either compound. Blood studies demonstrated eosinophilia (up to 15%) in 67 out of 101 blood smears. This was not considered significant since medication was continuous, and the blood findings were probably indicative of a mild allergic reaction; furthermore, it is believed that allergy is more readily elicited in a tuberculous subject.

On an equimolecular basis, it could be concluded that the diglucoside was about three times as effective as the USP preparation.

6-16 YEARS GROUP

(Hospitalized). Both laxatives and enemas had been used previously in this group of twenty-five tuberculous patients. As before, diet was standard during investigation period (eight weeks) and control period. Nine subjects were bedridden; sixteen had bathroom privileges.

Medication was initiated with the diglucoside for a group of twelve children; the other group of thirteen received the USP preparation; the first cycle was of one month's duration since optimum dosage was not established in the first two weeks. Thus the comparative study was based on the second month's investigation, when the compounds were alternated at two-week intervals. The initial dose of diglucoside was 1/12 grain, which was increased at two or three-day intervals until the optimum dose of 1 to 2 grains was reached; the initial dose of phenolphthalein was 1/8 grain, and optimum dosage was arrived at in a similar manner.

(in grains)	Diglucoside	USP Phenolphthalein
Total dosage during period of study	430	431½
Total number of bowel movements	246	246
Actual dose per patient	1/12 - 2	1/8 - 2
AVERAGE EFFECTIVE DOSE	1 - 2	1 - 2

Though cramps and nausea were complained of in several cases with either preparation, repeated doses failed to produce like symptoms.

Urinalysis occasionally demonstrated phenolphthalein in the urine after 2 grain doses of each compound; however, there were no pathological changes due to phenolphthalein, and no skin reactions were observed even with large doses.

It can be concluded from this study that the diglucoside was approximately twice as effective as the USP preparation *on an equimolecular basis*. Children at this age level tolerated larger doses than had been expected.

16-75 YEARS GROUP

(Hospitalized). Only four of these subjects were in the sixth and seventh decades. The study was based on two months' observations of 50 patients with varying degrees of constipation. Diet was standard throughout investigation. Dosage, in grains, was as follows:

	Diglucoside	USP Phenolphthalein
Total dosage during period of study	652 2/3	868½
Total number of bowel movements	1896	1822
Actual dose per patient	1/2 - 2*	1/2 - 2**
AVERAGE EFFECTIVE DOSE	1/2 - 1/2	1/2 - 1
	*(42% required 1/6)	*(60% required 1/2)

NOTE: The four subjects in the sixth and seventh decades required the upper limits of both preparations.

No reactions due to sensitization from previous use of either compound could be observed, nor any evidence of increased or decreased tolerance. In cases in which renal disturbances were already present, urinalysis demonstrated no irritation due to either compound; in the remainder, the occasional albuminuria and pyuria was considered clinically unimportant (specimens were not catheterized). Phenolphthalein was not detectable in the urine. Blood and stool examinations were negative.

In this study, the diglucoside proved two to four times as efficacious as the USP phenolphthalein preparation, *on an equimolecular basis*.

OLD AGE GROUP (56-86 YEARS)

(Hospitalized). This report is based on two months' observation of thirty patients (only two of whom were in the fifth decade), most of whom were senile and suffering from some type of vascular disease and varying degrees of atonic constipation. As before, diet was controlled, and the preparations were alternated at bi-monthly intervals. Dosage, in grains, was as follows:

	Digluco-side	USP Phenolphthalein
Total dosage during period of study	600	511.5
Total number of bowel movements	590	531
Actual dose per patient	2.14	1.78
AVRAGL EFFECTIVE DOSE	1 - 6	1/2 - 4
(28 subjects only included in statistics)		

In this study delayed action was noted with both preparations, and no cumulative effect with the digluco-side in spite of large doses. No skin reactions were observed. Urinary findings were negative; it was

CHART III

Age Group (years)	Range of Effective Dose of Phenolphthalein beta digluco-side	Period of Observation
1 1/2 - 5	1/12 - 1/6 grains	six months
5 - 8	1/12 - 1/4+ grains	eight weeks
6 - 16	1 - 2 grains	eight weeks
16 - 75	1/6 - 2 grains	two months
56 - 80	1 - 2 grains	two months

noted that on administration of 1 grain of the USP drug every third day, phenolphthalein was detectable in the urine; such was not the case with the digluco-side until the dose reached 2 grains. Stool examination gave no evidence of intestinal irritation, and the blood studies demonstrated no pathological findings due to either preparation. On an equimolecular basis, the digluco-side was 1.7 times as effective as the phenolphthalein USP, for this group.

The evaluation of phenolphthalein beta digluco-side by clinical testing with five age groups (156 subjects) may be summarized as follows:

CLINICAL TESTING OF COMPLETE ELIXIR FORMULATION

Drug Administration during FIRST CYCLE OF TWO WEEKS (grains)					Drug Administration during SECOND CYCLE OF TWO WEEKS (grains)					Drug Administration during THIRD CYCLE OF TWO WEEKS (grains)				
PBD	Elixir	USP	Total	Bowel Movements	PBD	Elixir	USP	Total	Bowel Movements	PBD	Elixir	USP	Total	Bowel Movements
A		1/2	15	173			1	21	57			1	16	56
B		1/2	12	80		68/100		19-1/3	74	1			30	74
C	1/2		15	81	1			29	67	1			30	78
D	1/2		12	68			1	26	72		68/100		20	68
E	35/100		10.5	94		68/100		20	109		68/100		20	102
F	35/100		10.5	106	1			30	108			1	15	54

The following re-charting of results demonstrates the comparative efficiency of the three preparations:

FIRST CYCLE OF TWO WEEKS					SECOND CYCLE OF TWO WEEKS					THIRD CYCLE OF TWO WEEKS				
factor = $\frac{\text{bowel movements}}{\text{grains administered}}$														
elixir	F	10.09	E	8.95	elixir	F	3.6	F	5.4	elixir	F	3.6	E	5.1
PBD	D	5.6	C	5.4	PBD	D	2.8	C	2.3	PBD	D	3.4	C	2.6
USP	B	5.3	A	6.0	USP	B	3.8	A	2.7	USP	B	2.5	A	3.5
Lxptl. Group														
Controls														

PBD — phenolphthalein beta digluco-side
USP — phenolphthalein USP

STUDY OF COMPLETE ELIXIR FORMULATION

Dr. Rosenthal compared the finished elixir formulation with an aqueous solution of digluco-side and with phenolphthalein (USP) in a group of twenty-nine tu-

berculous children, ranging in age from 8 to 15 years. The group was subdivided into six sections, designated alphabetically. The drug under study was administered every other day, except Saturdays and Sundays; the three preparations were rotated among three groups — B, D, and F — at two-week intervals while each of the three remaining groups — A, C, and E — received a single preparation for the duration of the experiment, serving as controls. The distribution of medication is shown in Chart IV. This cross-checking eliminated the need of prolonging the time of study in order to allow rest periods between changes of drugs.

It will be noted that in the second and third two-week periods the number of bowel movements did not increase proportionately to the increase in dosage. It was assumed therefore that the original lower dose was the optimum dose until subsequent trials indicated that the variation was probably due to a change in response; there was no opportunity to check the validity of this explanation.

The extent of uniformity in results between the experimental group and controls justified the procedure of shifting groups from one preparation to another.

The only significant finding was that of prevalent eosinophilia (up to 14%). It will be recalled that this was noted also in another tuberculous group (3 to 8 years) and was assumed in that study to be due to prolonged and continuous administration of the drugs. In this group, however, administration was not as in-

CHART NO. IV

tensive and the only explanation which can be offered is that possibly latent allergic states (as manifested by the eosinophilia) are more easily evoked in tuberculous patients. Otherwise there were no changes attributable to any of the preparations.

CONCLUSIONS

On an equimolecular basis, the relative efficiency of the preparations might be stated as follows:

	USP		
	Elixir	Phenolphthalein	Diglucoside
1st cycle	4	2	1
2nd cycle	4	2	1
3rd cycle	3.4	2	1.4

The elixir proved superior to the aqueous diglucoside preparation to an unexpected degree; apparently the components of the elixir, though possessing in themselves no laxative effect, enhance the action of the diglucoside.

The unpleasant side effects noted in previous studies were completely absent in this group, and all three preparations proved to be entirely safe. Of importance in pediatrics is the fact that the elixir was well received by the children.

The elixir was also studied clinically by Dr. Blatt in a group of thirty-eight children ranging in age from 7½ to 17 years; all were ambulatory and of the group

SCHEDULE OF PROCEDURE
CLINICAL TESTING OF COMPLETE
ELIXIR FORMULATION

PERIOD	No. Days	Drug in Group A	Drug in Group B
First Observation	14	0	0
Test for Minimal Effective Dose	7	USP (powder) ¼-1 gr. daily	USP (powder) ¼-1 gr. daily
First Drug Period	14	USP* (powder) 1 gr. daily	PBD (aqueous soln.) 1 gr. daily
Rest Period	4	0	0
Second Drug Period	14	PBD (aqueous soln.) 1 gr. daily	USP (powder) 1 gr. daily
Rest Period	4	0	0
Third Drug Period	14	PBD elixir 1 gr. daily	PBD elixir 1 gr. daily
Rest Period	4	0	0
Last Drug Period	14	USP (powder) 1 gr. daily	PBD (aqueous soln.) 1 gr. daily
Final Observation	7	0	0

*Results discarded because the deviation in phenolphthalein content was too great.

PBD — phenolphthalein beta diglucoside

USP — phenolphthalein USP

CHART NO. V

COMPARATIVE EFFECTIVENESS OF PBD, ELIXIR, AND USP, IN EQUIMOLECULAR WEIGHTS*
(Groups A and B are composed of 19 children each)

	PBD				Elixir PBD				USP			
	Grains Given	USP Equiv.* Grains	No. Stools	Stools per gr. Equiv.	Grains Given	USP Equiv.* Grains	No. Stools	Stools per gr. Equiv.	Grains Given	USP Equiv.* Grains	No. Stools	Stools per gr. Equiv.
Constipated												
A	252	124.24	155	1.24	252	124.24	204	1.64	252	252	193	0.75
B	336	165.65	304	1.83	168	82.82	160	1.94	168	168	118	0.70
Normal												
A	14	6.90	11	1.59	14	6.90	24	3.47	14	14	30	2.15
B	196	96.63	273	2.82	98	48.31	129	2.69	98	98	128	1.30
Total												
A	266	131.14	166	1.26	266	131.14	228	1.74	266	266	223	0.83
B	532	262.28	577	2.19	266	131.14	289	2.20	266	266	246	0.92

*The molecular weight of phenolphthalein is 318.31, while that of phenolphthalein beta diglucoside is 642.59

On a molecular basis, the beta-diglucoside contains 49.3% phenolphthalein.

COMPARISON OF EFFECTIVENESS OF PBD, ELIXIR PBD, AND USP IN
NORMAL AND CONSTIPATED CHILDREN

DRUG	NORMAL (8)		CONSTIPATED (30)	
	Number of Stools per grain (Equimolecular weight)	Ratio of Effectiveness to USP	Number of Stools per grain (Equimolecular weight)	Ratio of Effectiveness to USP
PBD	2.74	1.94:1	1.58	2.13:1
ELIXIR PBD	2.77	1.96:1	1.75	2.39:1
USP	1.41	1:1	0.74	1:1

CHART NO. VI

thirty were constipated and eight were normal. The children were divided into two groups of nineteen each. The schedule of procedure can best be shown graphically (see Chart V); Chart VI shows the comparative effectiveness of the three preparations in both normal and constipated subjects.

Untoward effects were more frequent in the constipated group and the symptoms occurred more often when the USP preparation was administered than with either the diglucoside or the elixir. Blood, stool, and urine studies revealed there were no significant findings due to any of the three preparations.

It will be noted that cathartic effect of the respective preparations was greater in Group B than in A, and this can be explained by the fact that there was a greater percentage of normal children in that group.

A significant observation made in this study is that the same dose of diglucoside is twice as effective in normal as in constipated children.

SUMMARY

A solubilized phenolphthalein laxative of low toxicity, the beta diglucoside derivative, is described, and the results of clinical investigations into its effectiveness, as measured against USP phenolphthalein, are recorded.

REFERENCES

- Caldwell, G. H. and Crane, A. W.: The Influence of phenolphthalein in intestinal movements. *Radiology* 13:403 (1929).
Ott, I. and Scott, J. C.: The action of phenolphthalein, cascara sagrada and ergot upon the intestinal movements. *Med. Bull., Phila.* 30:90 (1908).

As far as is known, phenolphthalein beta diglucoside is the only colorless, odorless, tasteless, water-soluble substance possessing laxative properties. While stable in solution, it is hydrolyzed in the intestine to liberate free phenolphthalein (this is not true of other water-soluble derivatives reported in the literature). When this free phenolphthalein is recovered, it is found to be as pure as the better grades of USP phenolphthalein. Its aperient action is mild, yet thorough, and persistence of such action for several days enables many patients accustomed to daily medication to reduce their requirements. The derivative has a distinct advantage in that it lends itself well to uniform distribution in solid or liquid form, thus permitting exact measurement in standard or fractional doses. Calculated on the basis of active principle contained, the effective dose of the diglucoside is about half that of phenolphthalein.

The elixir is a laxative which is both safe and palatable and because of its form, it enables rapid and complete absorption and greater uniformity of response, hence permitting smaller dosage.

The range of effective dose was determined in seven clinical studies, covering all age groups, in five of which the diglucoside was compared with USP phenolphthalein, and in two of which the elixir formulation was studied.

- Tunncliffe, F. W.: Synthetic purgatives: the purgative action of dihydroxy-phthalophenone (phenolphthalein, purgen). *Brit. Med. Jour.* 2:1224 (1902).
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HISTORIAL NOTE

Phenolphthalein beta diglucoside is a water-soluble cathartic, first synthesized in the laboratories of the Bristol-Myers Company, and the clinical studies reported herein were sponsored by them. The new derivative is stable in the pH range, 4.5 to 8, and is incorporated in a pleasantly flavored elixir. The process for its commercial production was developed by Arthur D. Little, Inc. and the Atlas Powder Company.

An extensive program on the toxicological evaluation of the drug was carried out by Dr. Frederick F. Yonkman (1938), then Associate Professor of Pharmacology, Boston University School of Medicine, with the cooperation of Dr. Charles F. Branch, who conducted the pathological studies. Results of the toxicological testing were con-

firmed by Dr. Maurice Rosenthal before initiation of clinical investigation. The clinical evaluation, which comprised comparison with USP XI phenolphthalein and determination of minimum dosage, was conducted under the direct supervision of Dr. Rosenthal and was supplemented by a similar evaluation of the finished elixir of phenolphthalein beta diglucoside; in this study patients in all age groups were included. The late Dr. Maurice Blatt⁴ made a special study of the elixir in the age group 7 to 17 years. All toxicological findings were more recently confirmed (1945) by Dr. Walter L. Mendenhall, Professor of Pharmacology, Boston University School of Medicine.

⁴Dr. Blatt was then Professor of Pediatrics at the University of Illinois College of Medicine and Chief of Pediatrics Division of the Cook County Hospital and St. Vincent's Orphanage.

Book Review

Parenteral Alimentation in Surgery. By Robert Elman, M. D., pp. 284, (\$4.50), Paul B. Hoeber, Inc., New York, 1947.

This is the first full-length presentation of a very important subject. Elman takes, as the six nutritional substances,—water, salts, protein, carbohydrates, fat and protein and devotes his book to the parenteral ad-

ministration, especially of the amino-acids, to surgical patients. "Surgery without starvation" increases operability, facilitates surgical procedures, minimizes post-operative complications and reduces mortality. The monograph, which was awarded the Quinquennial Samuel D. Gross Prize of the Philadelphia Academy of Surgery for 1945, should be studied carefully by all surgeons.

Abstracts of Current Literature

(Microfilm copies of papers may be obtained from the Microfilm Service of the Army Medical Library at 25c per each complete article, not exceeding 25 pages in length—and 10c for each additional 10 pages or fraction thereof. Prepayment is not requested. Remittances may be made with subsequent orders and in such manner as found most convenient. Address—Microfilm Service, Army Medical Library, Washington, D. C.)

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CLINICAL MEDICINE

BOWEL

FLETCHER, J. P., DOUGAN, A. AND SAMMON, G. K.: *Incidence and treatment of amebiasis* (Canad. Med. Assoc. J., v. 55, p. 278, Sept. 1946.)

In temperate climate dysentery is not a marked symptom in people infected with *Endamoeba histolytica*. The incidence of the disease was high among war prisoners of the Japanese kept in both Hong Kong and Japan. Veterans of the Mediterranean and European camps also show a high incidence of infection (30 and 25 per cent respectively). Unless spread of the disease is checked now it will spread in North America. Attempts to arrest the disease are recommended even in cases showing no present activity. Emetine is effective for the trophozoite form but not the cystic form. Chiniofon and the arsenical compounds are recommended as the most effective drugs. In cases of recently acquired amebiasis a 95 per cent cure was obtained with a single course of treatment with chiniofon. Rectal and colonic ulcerations responded well to retention enemas of the drug.—F. X. Chockley.

ROBINSON, R.A.: *Importance of diagnosis of asymptomatic amebiasis*. (Southern Med. J., v. 39, p. 876, Nov. 1946.)

In only about 10 per cent of the cases infected with *Entamoeba histolytica* are there episodes of dysentery. Consequently the true nature of the infection is not discovered in most of the cases until there ensues a critical attack or until the diagnosis is made at autopsy. In about half of the cases the liver may be found to be

involved and in some cases the cecum is involved. Examination should be made of three normally passed stools, and if the organism is not found attempts should be made to obtain specimens through the sigmoidoscope following a saline cathartic and saline enemas. The zinc sulfate centrifugation-flotation procedure is recommended for separation of the organism from fecal matter. A course of emetine injections with reexamination of the stools within six months is suggested.—N. M. Small.

PANCREAS

ROSENFELD, G. B. AND BAXTER, W. J.: *Fibrocystic disease of the pancreas in infants*. (Canad. Med. Assoc. J., v. 54, p. 438, May, 1946.)

Cystic fibrosis of the pancreas is the basis for the clinical syndrome designated as fibrocystic pancreatic disease seen in children. While the secretion of insulin is undisturbed the secretion of enzymes by the acinar cells is greatly reduced or abolished. Fecal fat is increased, and is largely in the free form although the gross appearance of the stool may be normal. The steatorrhea is accompanied by a loss of the fat-soluble vitamins A and D. Metaplasia of the bronchi and lung, with reduced resistance to respiratory infections, are due to the vitamin A deficiency. The pathogenesis of the disease is not known but the defect probably is embryologic. The children generally die within the first year but some children with signs and symptoms of coeliac disease having also chronic bronchitis or bronchiectasis may live a few years.

The authors present four cases, each under 4 months of age. Three of the patients died and autopsy findings

confirmed the diagnosis. The diet recommended should be high in protein and carbohydrate. The use of banana flakes as a source of carbohydrate and as a means of flavoring the food formula is recommended. Pancreatin is given before each feeding. Percomorph oil as a vitamin source is advocated. To increase intestinal tone and thus aid intestinal absorption the authors suggest prostigmin. Penicillin in large doses is used to combat the pulmonary infection which is commonly present. — Wm. J. Snape.

BARBOSA, JORGE DE CASTRO, AND WAUGH, J. M.: *Heterotopic pancreatic tissue, clinically significant, in the gastric wall of a boy six years of age.* (Proc. Staff Meet. Mayo Clinic, v. 22, p. 25, Jan., 1947.)

Pancreatic heterotopia signifies the presence of tissue similar or identical to normal pancreatic tissue but without anatomical or vascular continuity. Previously 41 authentic cases, 25 of which were clinically significant, have been reported in the literature. However, heterotopia is fairly common at post-mortem, occurring in 1 out of 500 autopsies. Only five children have been reported with heterotopic pancreatic tissue located in the stomach—whereas in the adult population 70 per cent of heterotopia is in the stomach. The heterotopic tissue may undergo any pathologic change that is found in the pancreas in its normal site. The symptoms produced are those of any gastro-duodenal lesion. Briefly this case reports a six-year-old boy who had gastro-intestinal complaints since the first year of life. The symptoms were umbilical pain without reference to food, but relieved by the genu-pectoral position and vomiting. Roentgenologic examination revealed a polyp in the pre-pyloric region. Physical examination and laboratory tests were irrelevant. At operation a pancreatic rest 1.5 cm. in diameter was excised with complete relief of symptoms. — Wm. J. Snape.

WALKER, H. A.: *Pancreatic cysts.* (Southern Med. J., v. 40, p. 180, Feb., 1947.)

Cases of pancreatic cysts were reported as early as 1830. Although the literature is not very replete with case histories, the condition is not very uncommon. At present cystic diseases of the pancreas may be classified under these four broad headings: retention cysts, cystic neoplasms or proliferative cysts, pseudocysts (or those resulting from degeneration or necrosis), and true pancreatic cysts. The benign cysts of the pancreas include congenital cystic disease, and cysts of the pancreas due to retention, blastogenic cysts, echinococcus cysts and dermoid cysts.

Walker reviews some of the recent literature pertaining to cyst formations and draws attention to the oft-repeated statement that the most common cause of cyst is chronic interstitial pancreatitis. Pancreatic cysts have been found in all ages and both sexes. The outstanding physical findings are discussed. — N. M. Small.

LIVER AND GALLBLADDER

UNFUG, G.: *Comparative clinical investigation of cholecystographic preparations.* (Radiol., v. 46, p. 489, May, 1946.)

Tetraiodophenolphthalein and priodax were compared in a series of patients. Priodax was found superior in that it gave better gall-bladder visualization more consistently, gave diarrhea and nausea less frequently, and was more pleasant to take. Absence of opaque shadows in the hepatic flexure (seen often with the older type dye) aided visualization by removing confusing issues. — Wm. J. Snape.

HAVENS, W. P. JR. AND MARCK, RUTH E.: *A comparison of the cephalin-cholesterol flocculation and thymol turbidity tests in patients with experimentally induced infectious hepatitis.* (J. Clin. Investig. 25, 816, Nov., 1946.)

Twenty-seven healthy male volunteers, 19 to 29 years of age, were infected by inoculation or by ingestion of the virus of epidemic infectious hepatitis. Their cephalin-cholesterol precipitation, thymol turbidity, and brom-sulfalin dye tests were at first found within normal range. The disease was divided into: 1. incubation (pre-febrile), 2. febrile (pre-icteric), 3. icteric (post-febrile), and 4. convalescent (post-icteric) phases. The tests were made on simultaneously drawn serum within two hours for the cephalin-cholesterol test and, in some cases for the thymol turbidity test, after dry frozen storage for 2 to 12 months (without loss of sensitivity to the test).

Generally it was found that the thymol turbidity test remained negative longer than the cephalin-cholesterol test, but that both were positive during some phase of the disease. Both tests were usually negative during the incubation period, and both were equally positive in the third or icteric phase. The cephalin-cholesterol flocculation also showed a quicker return to normal. — Wm. D. Beamer.

DUNSKY, I.: *Congenital biliary cirrhosis.* (Amer. J. Dis. Child., v. 71, p. 150, Feb., 1946.)

Jaundice, ascites, and esophageal varices hemorrhages are usually the first (and serious) signs of liver cirrhosis. Early differentiation between hepatic and extrahepatic disease is necessary to obtain the benefits from instituting dietary treatments as soon as possible. Disturbed carbohydrate metabolism as shown by the intravenous tolerance test is indicative of liver disease. The author presents several cases in infants to illustrate congenital biliary cirrhosis. An intravenous tolerance test was carried out on an infant two months of age: previously this test had been reported as having been done in adults only. Several unusual features of congenital biliary cirrhosis are discussed. — H. Stilyung.

The Obese Patient. A Statistical Study and Analysis of Symptoms, Diagnosis and Metabolic Abnormalities. Sex Differences—Treatment.

By
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Obesity itself is not a disease and should not be treated as such. Many obese subjects are healthy; most of them are not. However, in spite of the absence of any demonstrable anatomic changes or abnormal dynamics in many of these individuals, we consider obesity an undesirable state. This is so, not only from the standpoint of the unaesthetic factors with their resulting adverse psychogenic effects, but more important is the well-established fact that the obese exhibit increased susceptibility to cardiovascular and metabolic diseases which increase morbidity and decrease the span of life.

Careful study of the obese who are apparently in good health often reveals subclinical disease directly related to the overweight. Obesity therefore, if only from the standpoint of preventive medicine, must be regarded as an abnormal and harmful state.

This discussion concerns an analysis of one hundred and ten office cases, ranging in age from 16 to 61 years, chosen consecutively from my records whenever obesity was a coincidental finding. All of them, ninety-five females and fifteen males had clinical and laboratory surveys with roentgenologic, gynecologic and orthopedic consultations when indicated. (1)

The laboratory studies included complete blood count and chemistry, sedimentation rates, icterus index, Van Den Bergh, blood calcium and phosphorus, oral glucose tolerance curve, serologic and precipitation tests, gastric analysis and Mosenthal renal function studies. When specifically indicated, additional studies including allergic survey, dye tests, blood phosphataes, cephalin flocculation and detailed hematologic studies were done.

SYMPTOM ANALYSIS:

Obesity was not a primary complaint in any of these cases. Table I lists the 26 symptoms in their order according to the frequency with which they appeared as subjective complaints. Thus first is fatigue, which was common to over 74% of the cases, followed in their order by nervousness 59%, digestive disorders 38%, muscle and joint manifestations 35%, headache 30%, irritability 29%, dyspnea on mild effort 20%, and so on.

These are exactly the symptoms that one would expect on the basis of the statistical diagnostic survey which follows. Often a symptom or group of symptoms is the result of a number of conditions independent of each other or interrelated. Thus, for example, tingling and numbness of the extremities can at once be referable to hematologic deficiency, nutritional factors and sensory nerve root irritation from orthopedic disturbances or vertebral osteoarthritic changes.

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TABLE I

FREQUENCY OF SUBJECTIVE COMPLAINTS, 110 CASES

1. Fatigue	74%
2. Nervousness	59
3. Digestive Disorders	38
4. Joint and Muscle Pains	35
5. Headaches	30
6. Irritability	29
7. Dyspnea on effort	20
8. Menstrual Disorders	14
9. Emotional Instability	10
10. Numbness and Tingling	9
11. Dermatological Disorders	9
12. Precordial Distress	8
13. Insomnia	8
14. Intolerance to Cold	8
15. Soreness of Mouth	8
16. Dizziness	7
17. Palpitation	7
18. Pruritus	6
19. Edema	6
20. Mental Depression	5
21. Frequent Colds	4
22. Craving for Sweets	4
23. Urinary Disturbances	3
24. Poor Memory	3
25. Hunger Spells	3
26. Somnolence	2

DIAGNOSTIC SURVEY AND ANALYSIS:

Table II lists the 24 diagnostic headings according to the frequency with which they appear on the clinical records.

TABLE II

DIAGNOSES IN ORDER OF TIMES FOUND, 110 CASES

1. Climacteric Syndrome	55%
2. Biliary Tract Disease	42
3. Hypothyroidism	35
4. Cardiovascular Disease	33
5. Musculo-skeletal and Arthritic Disease	33
6. Nutritional Deficiency	26
7. Anxiety and Psychoneurotic States	21
8. Endocrinopathia	18
9. Dermatologic Disease	17
10. Premenstrual Tension	6
11. Diabetes Mellitus	5
12. Functional Digestive Disorders	5
13. Migraine	4
14. Pyelitis	4
15. Nephrolithiasis	4
16. Nephroptosis	4
17. Fibromyoma	3
18. Functional Amenorrhea	2
19. Duodenal Ulcer	1
20. Sterility	1
21. Pancreatic Disease	1
22. Gout	2
23. Cataract	1
24. Narcolepsy	1

1. Climacteric Syndrome: This heads the list with 55% and includes both male and female. The condition is much more frequent than this would indicate because the number of cases in the group above thirty-five

years of age is 68 out of 110 bringing the percentage up to 71%. This diagnosis was made only in the presence of characteristic clinical evidence including vasomotor disturbances, nervousness, irritability, emotional instability and constitutional inadequacy, extremely low estrogen levels and in the male the added factor of significant diminution of libido or potentia or both. A survey of another 100 clinical cases, all non-obese, reveals that the clinical diagnosis of the climacteric on the same basis can be made only in 18% of the group. The indications are that obesity is a definite factor in aggravating the climacteric syndrome and in inducing the clinical state of it, when it would otherwise remain symptomatically subclinical.

2. Biliary Tract Disease: This is second with 42% and includes the cases with cholecystitis, cholelithiasis, poor concentration capacity of the dye, delayed emptying, hepatic insufficiency and liver disease. The diagnosis was based on positive roentgenologic findings with significant alteration from normal in one or more of the tests including the icterus index, quantitative Van Den Bergh, urobilinogen, blood lipids and cephalin flocculation. In a similarly chosen group of 100 non-obese cases, the diagnosis of biliary tract disease on the same criteria was made in only 12% of the cases. The presence of biliary tract disease in the obese is therefore not a mere coincidence occurring almost four times as frequently as in the non-obese. In addition, many of the non-obese with biliary tract disease give a history of having been overweight in previous years.

3. Hypothyroidism: The finding of a low B.M.R. was in itself ignored unless there was associated clinical evidence of thyroid deficiency, especially the typical fat distribution of hypothyroid obesity, intolerance to cold, dryness of the skin, changes in the nails, diminished physical reserve, increased glucose tolerance, poor memory and mental retardation. It is interesting to note that the finding of extremely low metabolic rates without subjective or objective manifestations of hypothyroidism was practically confined to the geriatric group. While thyroid deficiency may be one of the primary factors in the evolution of obesity, it can be secondary to the obesity on the basis of depletion from excessive demand, reduced physical activity of the obese and pituitary and insulin factors concerned with high carbohydrate, high fat and low protein diet so common with obese people. In the similarly chosen non-obese group, diagnosis of hypothyroidism on the same basis could only be made in 8% of the cases, compared to 35% of the obese group.

4. Cardio-Vascular Disease: This group, numbering 35%, includes essential hypertension, hypertensive cardio-vascular disease, hypertensive retinopathy and nephropathy, coronary insufficiency and coronary disease. The similarly chosen non-obese group showed this condition on the same evaluation basis to occur in 10% or less than one-third the frequency. Recently, Levy and White (2) in an analysis of 22,741 officers the United States Army from the standpoint of overweight, concluded that overweight alone showed signifi-

cantly higher rates for later sustained hypertension and for retirement with cardio-vascular renal disease, than did a control group and that when in addition to the overweight, transient hypertension and transient tachycardia were present, the rate of the development of sustained hypertension was twelve times as great as in the controls; in the case of retirement with cardio-vascular-renal disease, the rate was four times as great.

The factors concerned in the markedly increased susceptibility of the obese to cardiovascular disease concern the disturbed lipid metabolism with hypercholesteremia, vascular degeneration with subendothelial cholesterol deposit, stress and strain with anoxia of the vessel walls and cardiac structure, depressed basal metabolism, water and chloride retention, nutritional factors, particularly protein deficiency, mechanical factors involving strain on the sinuses of Valsalva and the coronary circulation, postural and orthopaedic factors which contribute to strain in the lower abdominal aorta at the bifurcation where internal atheromata are most frequently seen and finally familial and constitutionally endowed factors which contribute the constitutional background for obesity and cardiovascular disease.

5. Musculo-skeletal and Arthritic Disease: This group, numbering 33%, embraces the fibrositic and bursal conditions, the arthritides including hypertrophic, degenerative, and the less frequent atrophic types and the intra-articular cartilaginous and ligamentous disturbances. Practically all subjects who have been obese for a period of years into middle life present definite evidence of abnormal posture with orthopaedic disturbances. Thus it is not uncommon to see these individuals with eversion of the feet, resulting in replacement of the physiological tripod support of the feet (the heel and the heads of the first and fifth metatarsals with adequate arches) by the characteristic bi-pod (the heel and the heads of the 2nd, 3rd and 4th metatarsals with sub metatarsal callosities, inevitable transverse widening of the foot with bunion formation, secondary circulatory disturbances of the feet with resultant ankle edema and varicosities). The feet are everted as though to get more leverage to support the pendulous abdomen which hangs down, the os calcis is often everted accompanied by genu valgum with inward angulation of the knees and knee ligamentous strain. They virtually walk on their knees and lumbo-sacral spine because of lowering of the center of mass. Pesplanus and lumbo sacral strain are the rule. Superimposed on this are the nutritional deficiencies, menopause, metabolic and circulatory factors, and in some instances focal infection, all of which contribute to the supervening osteoarthritic, cartilaginous and intra-articular structural damage. Sensory nerve root irritation and compression contribute to the pain, numbness and tingling of the extremities.

6. Nutritional Deficiency: Twenty-six percent revealed evidence of clinical or subclinical deficiency states. The diagnosis is based on the finding of tongue changes, a beefy red tongue or marked smoothness

from papillary atrophy, swelling and indentation of the margins or fissuring with glossitis. Eye manifestations include sensitiveness to light, nyctalopia, xerophthalmia, corneal epithelial dystrophy, lenticular and vitreous opacities and in older people, marked scleral capillary congestion with dryness. Indeed, I have seen a degree of scleral injection giving an appearance to the sclera of fresh cut beef and a miraculous response to high protein and adequate vitamin therapy. Other factors include aches and pains, tender muscles, particularly those in the calves of the legs, burning feet, edema, tingling and numbness, and scattered paraesthesias, edema, fatigue and loss of interest. Most of the obese are "carbohydrate specialists" and over the years condition the pancreas to rapid and excessive elaboration of insulin resulting during the first phase of their obesity in rapid utilization of sugar, hypoglycemia and therefore increased appetite with craving for food, particularly sweets. With progressive depletion of the insulin reserve and with a maintenance of the obesity, the supervening years bring hyperglycemia with pre-diabetic or actual diabetic states. While many of the subjects have an inadequate protein intake, those taking adequate dietary protein with excess carbohydrate give themselves so much immediately available carbohydrates that the body utilizes the carbohydrates first and defers the more difficult task of breaking down the proteins into the average 60% carbohydrate with the result that a large portion of the proteins passes on before it can be utilized. The result is therefore a protein deficiency, hence the saying "the fat are literally starving to death". The frequent finding of biliary tract disease and hepatic insufficiency as previously discussed are important contributory factors to the deficiency state of the obese. Whipple (3) has shown that the liver which receives the amino acids performs most of the work of protein synthesis; most of the plasma proteins emerge from the liver cells and can be utilized for all or almost all of the protein requirements. Thus the liver stores protein or releases fabricated protein and is therefore a potent factor in maintaining dynamic equilibrium between protein reserve and wear and tear.

7. Anxiety and Psychoneurotic States: Twenty-one percent of the cases showed evidence of some form of anxiety or psychoneurotic state. While this is not entirely unexpected in the older group, of whom 71% had menopausal symptoms, the condition is relatively more frequent and more significant in the younger groups, particularly the adolescent and post-adolescent in whom the mental attitude is adequately portrayed by the term "social anxiety". This younger group, especially the female, is very introspective, self-conscious and ill at ease, their social adjustment is inadequate and they manifest vasomotor disturbances, headache and functional digestive disorders; many of them have amenorrhea, or hypomenorrhea or dysmenorrhea, aggravated by an associated pre-adolescent endocrine imbalance. Like in the older group the anxieties and neurotic constitution stir up an inward restlessness from frustration, disappointment and unfulfilled desires; subconsciously, they sense the physical aversion

of their mates, leading to a sense of insecurity. They cannot rationalize on the cause of their nervousness and will rarely admit that the basis of their complaints can be the obesity. Their constant turmoil is a major factor in the rapid utilization of glucose which accounts in part for the extremely rapid glucose tolerance curves and they learn very early that frequent nibbling of carbohydrates brings them relaxation and well being. Actually, the brain is the only organ in the body which is incapable of utilizing anything but sugar for energy while other tissues are capable of using both protein and fat.

8. Endocrine Aspects: Too much emphasis has been placed on the role of the endocrines in obesity. In this series 18% could be classified into certain accepted endocrinopathic groups, on the basis of their measurements, fat distribution, genital development and configuration, hair distribution, the character of the skin, the mental and intellectual status and certain laboratory studies. Pure Frohlich's disease is very uncommon, but there were several Frohlich-like types, other mild adipose genital dystrophies, two cases of Dercum's disease and others showing thyroid, pituitary and gonadal dysfunction either alone or in combination. Proper classification of type is of value in the pre-adolescent states where adequate substitution or stimulation therapy is of great importance; after adolescence, it matters little, merely because the preadolescent glandular status determines the configuration and fat distribution, and the treatment with some exceptions is almost exclusively by curtailing food intake.

9. Dermatologic Disorders: Skin conditions were practically confined to those over forty years of age and were observed in 17 percent of the cases. There were 3 cases of xanthoma diabetorum, 2 of necrobiotic lipoidica diabetorum, 7 of dermatitis of the legs with ankle edema, 4 of atopic dermatitis with toxic purpura, 4 of varicose ulcers with secondary dermatitis and pigmentation and 1 of diabetes bronze. It is apparent that the high incidence of dermatologic disease in the older obese is referable to the associated high incidence of diseases of metabolism, nutritional deficiency with hypoproteinemia and cardiovascular disease.

ANALYSIS OF LABORATORY FINDINGS— METABOLIC ABNORMALITIES

It has been reported that metabolic abnormalities in obesity are inconsistent and of no importance (4, 5, 6, 7.) Unfortunately, this assumption is based on the study of a single case or on the mean of a statistically insignificant series including the study of blood lipids on three cases, the respiratory quotient on seven and the specific dynamic action of proteins on seven obese patients. On the contrary, metabolic abnormalities are statistically so common in the obese as to assume profound importance. Thus the findings in this series of 110 unselected office cases are summarized in Table III and it is interesting to note that the results confirm very largely those recently reported by Goldzieher and associates (8) who carried out metabolic studies on an

adequate series of 100 consecutive unselected cases of obesity and another 100 cases showing some clinical evidence of pituitary disease.

TABLE III
METABOLIC AND CLINICAL LABORATORY ANALYSES

		Female	Male
1. Glucose Tolerance			
Normal	- - - - -	19 percent	26 percent
Rapid	- - - - -	65 percent	60 percent
Prediabetic or Diabetic	- - - - -	16 percent	14 percent
2. Renal Function—Mosenthal			
Normal	- - - - -	52 percent	79 percent
Increased Night Output	- - - - -	34 percent	15 percent
Specific Gravity Fixation	- - - - -	14 percent	6 percent
Av. 24 hr. Chloride Excretion	- - - - -	7.9 grams	9.0 Gms.
Av. 24 hr. Urea Excretion	- - - - -	15.5 Gms.	19.8 Gms.
3. Cholesterol			
Normal	- - - - -	30 percent	48 percent
Above 200 mgs.	- - - - -	70 percent	52 percent
4. B. M. R.			
Normal	- - - - -	49 percent	50 percent
Below Minus 12 percent	- - - - -	51 percent	50 percent
5. Gastric Acidity			
Normal	- - - - -	29 percent	16 percent
Hyperchlorhydria	- - - - -	53 percent	67 percent
Hypochlorhydria	- - - - -	18 percent	17 percent
6. Uric Acid			
Normal	- - - - -	79 percent	51 percent
Above 3 mgs.	- - - - -	21 percent	49 percent
7. Blood Picture			
Normal	- - - - -	48 percent	100 percent
Hypochromic	- - - - -	50 percent	None
Macrocytic	- - - - -	2 percent	None

1. Glucose Tolerance: The majority of cases show abnormal glucose metabolism which is more common in females than in males. In both sexes, rapid tolerance curves occur about four times as frequently as do the pre-diabetic or frank diabetic. This finding is understandable and throws some light on the pathogenesis of diabetes particularly in the obese. In addition to the associated factors in the obese of thyro-pituitary, thalamic and nervous influences, and the ability of the excess fat to take up sugar, there is the problem of frequently strained liver function effecting glycogen function, diminished storage capacity and indirectly the insulin tolerance. Of particular importance is the conditioning of the pancreas to hypersecretion of insulin in response to a long standing excess carbohydrate food, intake which in the static phase of the obesity contributes largely to the rapid curves and in the later stages to insulin depletion with frequently true diabetes.

2. Renal Function, Salt and Water Balance: All patients had Mosenthal renal function study (9) with determination of the 24 hour chloride and urea elimination and specific gravities of two hour specimens taken during the day and of the pooled twelve hour specimen during the night. Normally, the night output is much less than the day output, and its specific gravity will be 1018 or above. The average normal chloride output is 10 to 15 gm. in 24 hours and the urea 20 to 35 gm. Impaired renal function was indicated by one or more of the following changes: (a) nocturnal polyuria, (b) low maximal specific gravity of the day specimens, (c) fixation of specific gravities in the low or high levels, (d) chloride or urea retention or both.

Judged by these criteria, about half of the female subjects show impaired renal function compared to 21 per cent of the males. All of the obese women without exception and the majority of the males show chloride and urea excretion levels below average normals, the means in the female being much lower (Table III). Similar findings are recently reported by Goldzieher (8).

Urea is the principal waste product of Protein metabolism and constitutes about one half of all the solids excreted. It is influenced by exercise and diet and by abnormalities in liver, thyroid and renal function and in fevers. A normal person on a low calorie adequate protein diet of 1 gm. per kilo, goes into nitrogen balance because the stores of fat, which are available for energy spare the body proteins. These factors together with the diminished physical activity, diminished metabolic rate, high carbohydrate and high fat diets contribute to the finding of the constantly low urea output in the obese.

The effect of the thyroid, the posterior pituitary and hypothalamus and the role of the adrenal cortex on salt metabolism are well known. These factors are more likely to be disturbed in the obese.

3. Cholesterol: Cholesterol which constitutes the blood sterols is the best index of the blood lipid metabolism; it shows the most significant changes in disease; it is most easily determined in the laboratory and is the best index of the level of lipemia. Levels above 200 mgs. were encountered in 70% of the females in this study compared to 52% in the males. This high incidence of hypercholesteremia in the obese is in keeping with the high incidence of biliary tract disease (42 per cent of the series) hypothyroidism (35 per cent) and diabetes (5 per cent).

4. Basal Metabolic Rate: The B.M.R. determination was below minus twelve per cent in 50 per cent of the entire group and averaged the same in both sexes. The rate varied between minus twelve to minus thirty-five.

5. Gastric Acidity: The majority of the cases show abnormal hydrochloric acid levels, with a greater incidence in the males of whom only 16% showed normal values compared to 29 per cent in the females. Hyperchlorhydria was more common in the males while hypochlorhydria was about equal in both sexes.

6. Uric Acid: Blood uric acid determinations above 3 mgs. per cent was significantly common in the entire group showing a larger incidence in the male group in which only 51 per cent had normal blood uric acid levels compared to 79% of the female group. This abnormality is doubly significant in view of the finding of only 2 cases of clinical gout in the entire series, although it may throw some light on the high incidence of musculo-skeletal and arthritic disease which was found in 33 per cent of the cases.

7. Blood Picture: Here is seen the greatest difference in the sexes. While 100 per cent of the male group had blood counts well within the normal limits, 52 per cent of the females had significantly low blood counts, predominatingly hypochromic and microcytic

with 2 per cent showing hyperchromic macrocytic pictures. This difference is in a great measure due to the physiological blood loss of the female in menstruation and depletion from pregnancy and the greater incidence of hemorrhoids. It would appear therefore that from the hematologic and nutritional standpoint that obesity is a greater hazard for the female. The finding of lymphocytosis as a symptom of obesity according to the recent report of Goldzieher (8), was not confirmed in this survey.

Additional laboratory studies showed results which were inconsistent and infrequent and therefore irrelevant to this study.

Treatment: It is apparent from this statistical survey that there can be no set routine for the treatment of the obese. Unless the treatment is individualized on the basis of thorough clinical and metabolic survey, including the endowed constitutional and personality analysis, a routine diet and drug program is not only inadequate but can be harmful. It is significant that the correction of a majority of the symptoms and the objective findings depends either entirely or in part on the correction of the obesity.

A. Psychotherapy: Success in the treatment of the obese patient depends largely on his cooperation. To achieve this, he must be given the proper insight into his condition with a clear understanding of the relationship of his specific abnormalities, to the excess weight. He should from the outset be impressed with the fact that we know of no drug which can of itself safely bring about a loss in weight and must therefore learn from the beginning to depend on his own control. He must be made to understand that the wilful imposition of the burdensome stress and strain of his excess poundage eventually leads to irreversible depletion of his cardio-vascular and metabolic reserves with musculo-skeletal damage and inevitably premature involutional and degenerative changes resulting in morbidity and decrease in the allotted span of life. He must resolve that the desire to achieve results must be greater than the desire to bask in the sunlight and ecstasy of gluttony. Patients often blame their obesity on their glands; they should be told that the glands do not have mouths which take in food. They complain of weakness and agonizing hunger and they should be told that it is not in fact a purposeful physiologic hunger but rather a nostalgia for the delightful consciousness of appeasing their gustatory desires. Here they can be told that their habits of carbohydrate over-indulgence has conditioned the pancreas to excessive elaboration of insulin which burns their sugar so rapidly that they become weak and hungry three hours after a meal, and that 60 per cent of proteins are gradually converted to sugar thereby sparing the insulin, maintaining more adequate nutrition and warding off hunger spells until the next meal.

Obesity, like alcoholism is often part of an escape mechanism. A great many of the patients in this group particularly the females (59 per cent) had some form of anxiety resulting from family, sex, business or other difficulty. They greatly underestimate their caloric

intake and forget about their constant nibbling. They must be made to understand that the excess food intake is largely subconscious and that it represents by substitution the fulfillment of some more important unsatisfied craving which on analysis is often quite incapable of ever being realized. It is therefore as essential to evaluate the personality problems of these patients as it is the physical and laboratory studies.

The psychotherapeutic approach is even of greater importance in the younger group in whom there are often associated hypogonadal factors, femininity or masculinization and delayed secondary sex characteristics. Thus the younger ones become retiring, seek the company of friends much younger, bite their finger nails, refuse to take school gym or swimming and escape after school hours into their rooms where they find comfort in reading and in candy and ice cream. The adolescent patients develop what has aptly been termed by Myerson a social anxiety. The realization that they have become wall flowers brings about an intense self consciousness and introspection which renders them socially inadequate and miserable in the presence of company, at which time they develop spasticity of the facial muscles, urinary frequency, headache, gas, hyperventilation with dizziness and other symptoms referable to disturbed and uncontrolled autonomic function. With proper insight, this condition is not difficult to correct.

B. Specific Therapy: Treatment of specific abnormal states in the obese is no different from that in non-obese patients with the exception that the response to treatment is much more satisfactory when normal weight is attained and frequently the reduction in weight is often the only measure needed to correct certain abnormalities. This is particularly true in the obese who are subjects of diabetes, hypertension and musculoskeletal disorders. The diabetic who is at least 30 per cent overweight and whose fasting blood sugar is not over 250 mgs. per cent may in most cases be assured that adequate weight reduction will in itself bring about normal insulin function without the need of taking insulin. This alone offers a great incentive and inspiration for cooperation and almost invariably the subject is gratifyingly rewarded by an insulin free life. Only in more severe hyperglycemia or the finding of associated diabetic retinopathy or impending acidosis is it necessary as a precautionary measure to incorporate insulin in the program and even many of these cases reach a point where eventually they can furnish sufficient native insulin for an economy materially reduced in size. All of the diabetics in this group had a parallel reduction in blood sugar with their weight loss and completed their programs without insulin and in normal carbohydrate balance. Undoubtedly an important contributory factor in these cases was the improvement in liver function with the fat free diet and large doses of the B complex, resulting in more adequate sugar storage and in restoring glycolysis. All of the obese hypertensives, who were at least 25% overweight, provided the hypertension was essential, had a reduction in pressure parallel with

their weight loss and completed their programs with blood pressures within the normal limits. The diastolic pressures were slower in coming down but in time reached normal levels. Those patients who showed hypertension, with nephropathy or retinopathy, or other manifestations of organic vascular damage including the coronary and encephalopathic group were not rewarded with any significant drop in pressure upon attaining normal weight although the reduction made it easier to control their symptoms with the usual measures, but more particularly they manifested an increase in the cardiac reserve with loss of troublesome dyspnea and often an improvement in kidney function.

The results in the relief of symptoms referable to the musculoskeletal system including the cases with fibrositis, lumbo-sacral strain, myalgias, pes planus and the periarthritides were very gratifying. Often the reduction of weight together with simple measures including a hard bed, curving exercise, inversion of the feet in walking to reestablish the physiological tripod of body support on the feet with the indirect effect on correcting the genu valgum and the everted os calcis, were quite sufficient to relieve the symptoms. Cases with established structural changes in the articulating structures and in the inter articular cartilages were in better condition to benefit from more specialized orthopedic care.

The group with biliary tract disease benefited by the improvement in liver function and by the alleviation of associated symptoms referable to the obesity. Four of the cases with cholelithiasis experienced an attack of biliary colic for the first time during their weight reduction regime. All cases undoubtedly became better risks in the event of necessary surgical intervention.

C. Drugs: The use of thyroid substance for the sole purpose of weight reduction is therapeutically unsound and often harmful. As in the non-obese its use is justified only in the associated presence of clinical manifestations of hypothyroidism. It is contraindicated in spite of a low metabolic rate in those with hypertension, cardio-vascular disease and vasomotor instability, particularly in the absence of subjective or objective signs of hypothyroidism. Any advantage that may be gained by its use is nullified by the objectionable undesired effects, especially the tachycardia, with increased cardiac load on an already depleted myocardial reserve, the undesirable increased elimination of nitrogen, the increased appetite, the nervousness and the sweating. The claims that thyroid has a specific diuretic action have not been substantiated.

Of great value in the therapy of the obese is the use of certain cephalotropic drugs in view of their desirable psychomotor effects. Without their use, the successful result in this series could not have been achieved. The drug was never used at the beginning of treatment, but after the first four weeks, with an initial average loss in the entire group of 12.6 pounds, it became apparent that in most cases the use of the drug was almost essential to the continued cooperation of the patient. The drug was introduced in the capsule without the patient's knowledge in order to prevent the individual from depending on an appetite inhibiting

factor in the medication. The patient reported increased urge to work and increased energy output with little or no fatigue, together with a sense of well being. All the patients were started with racemic amphetamine averaging 10 mg. one half hour before lunch and dinner. Subsequently, the drug was replaced by d-Desoxyephedrin hydrochloride in the form of Desafrin. It was demonstrated that with this dextro form of amphetamine, a dose of around 6 mg. was as effective as 10 mg of the racemic form and that the undesirable peripheral effects obtained with the racemic form of d-Desoxyephedrine were significantly minimized or entirely absent. Similar results are reported by Davidoff (12). The pharmacodynamic difference is perhaps largely explained by the reduced dosage necessary to bring about the same central effect.

With the racemic form, most of the patients required an average of three-eighths grain of phenobarbital with each dose, whereas it was usually not necessary to use sedation when the dextro-amphetamine was employed in doses not exceeding 6 mg. twice daily, except where sedation would be indicated in similar conditions in non-obese patient. It can be stated unequivocally that in no case of essential hypertension did the drug cause an elevation of blood pressure and that in spite of its use in adequate dosage the blood pressure, as previously mentioned, ran a parallel reduction with the weight loss. In most of the group showing hypertensive cardiovascular disease, the weight reduction did not as a rule result in significant reduction in blood pressure. Neither did the use of the drug in these cases bring about any increase in blood pressure. In this connection, it is interesting to note that Ivy and Goetzel (10) revised the pharmacologic and therapeutic literature on the drug, including its use in psychiatric conditions. It can be further stated that in no case in this group was there any evidence of addiction to the drug. Patients are not told that they are receiving a drug for appetite inhibition and the drug is intermittently deleted without their knowledge. Occasionally upon deletion they will complain of a let down but this complaint is of very short duration and at this stage the weight is sufficiently reduced as to in itself bring up the muscular and circulatory reserve and feeling of well being and gratification at their accomplishment.

Constipation, resulting from the diminished bulk of a restricted diet together with the peristaltic inhibition of the drug, was not an infrequent complaint and was usually controlled by incorporating with the capsule 2 or 3 grs. of Ketocholanic acids (Triketol).

The use of atropine for its appetite inhibiting effect is objectionable because of its uncomfortable drying effect, mydriasis and increase in pulse rate. It was not found necessary to use it in this group, except where its action was specifically indicated.

Additional medication indicated for specific conditions and deficiencies is incorporated with the Desafrin. Thus to the capsule which is given before lunch and dinner may be added quinidine, digitalis, aminophyllin, etc. with good doses of thiamin, riboflavin or nicotinic acid. Hematinics are given if indicated and

the nutritional and vitamin deficiencies are supported by giving the natural factors as for example, yeast and vitamin B Complex liquid with crude liver extract which is a potent source of natural B, equal parts, a tablespoonful twice a day.

The subjects with significant disturbance of water or salt metabolism were studied from the standpoint of primary water and/or salt retention, associated adrenal cortical and other hormone effects, and reduction of colloid osmotic pressure from hypoproteinemia. Where indicated, adequate water elimination was obtained with mercuzanthin preferably orally in the form of 1 or 2 tablets before breakfast for 4 or 5 days and repeated at indicated intervals.

D. Diet and Exercise: The object of the diet is to obtain an effective reduction of energy intake which together with increased energy output, are the only measures required to accomplish safely a worthwhile weight reduction which is lasting. Handing a patient a printed detailed 600 to 900 calories diet has in most cases been unsuccessful. The patient is given a brief lecture on the principles of diet as they effect his condition. Blood and flesh are proteins derived from animals and protein is necessary for the replacement of the wear and tear. Carbohydrates, which are so excessive in the obese patients' diet, are merely a source of energy and they are told that excess carbohydrate brings about an outpouring of insulin which rapidly burns the carbohydrate resulting in a lowering of the blood sugar three hours after meals to a level where it should be in six hours, resulting in lack of energy and hunger followed by uncontrolled nibbling between meals and the great desire for sweets. They are told that 60% of the proteins are converted to sugar gradually, and that the gradual budgeting of the sugar into the blood, supplies at no time an amount of sugar which will tease out the insulin. Therefore they can maintain an adequate blood sugar level with sufficient energy for six hours until the next meal, without weakness, without nibbling, and without prematurely depleting the pancreas of insulin, thereby conserving their reserve and preventing a diabetic state which often follows in later years. They are told that there is no place for fat in the diet during the reduction program. Briefly, the patient is told to have an average serving of a protein food with every meal, taking his choice of meat, fish, poultry, any kind of cheese, jello, milk and eggs. Fats, including fat on meat, mayonnaise, olive and salad oils are interdicted and also the sweets, candy, jelly, potatoes, corn, cereals and the flour containing foods embracing bread, cake, pie, pastry, noodles, rice, spaghetti and vermicelli. It is compulsory that they take three meals a day. Breakfast for example, consists of fruit or juice, one egg, (a hard boiled egg is preferable because it is satisfying without bread) one crisp slice of bacon, a glass of skimmed milk and coffee with a little sugar, if desired or saccharine. Lunch may consist of a good portion of cheese or other protein, two crackers, a glass of tomato juice or skimmed milk and a little fruit if desired. Dinner consists of any lean meat, or fowl

or fish, one vegetable with butter sauce drained off, a salad without dressing, (mineral oil dressing is allowed) a glass of skimmed milk, and for dessert a custard or junket or jello or fruit. If hungry between meals, they may chew 6 or 7 malted milk tablets which of course are mostly protein. Adding salt at the table is disallowed as are heavily salted foods like herring and anchovies.

This program is highly flexible and is adaptable to the relatively healthy obese as well as to the ones with metabolic or degenerative disease. The patient must record his weight daily and is put entirely on his own with instructions to sensibly decrease the size of portions if the weight loss falls short of 2 pounds a week. It is remarkable how well they cooperate when trust is placed in their own intelligence and control. The program amounts to around 900 calories, the diet is satisfying, it results in decreased energy intake, adequate nutrition and positive nitrogen balance. Furthermore, it definitely controls the functional hypoglycemia which is so common in obese patients.

The matter of exercise which is so important for increasing energy output is a very individual matter. Many of the obese patients, obese for years, have already reached the limit of their cardiac reserve and especially in the hypertensives with cardio-vascular disease, exercise is contraindicated. These patients get sufficient exercise in their daily work and must compensate for their necessary limitation of physical activity and lessened energy output, by a stricter diet, in order to adequately curtail the energy intake. There is no objection to passive exercise and massage. The advertised gymnastic emporia while safe for the younger and relatively healthy obese, is a menace to the middle-aged group, particularly those with cardio-vascular strain and degenerative musculoskeletal and arthritic disease.

E. Endocrine Therapy: It has already been stated that the use of thyroid for weight reduction is definitely contraindicated and irrational even in the presence of a low metabolic rate, except where there are definite subjective and objective manifestations of hypothyroidism. However we cannot agree with Duncan (11) and Evans, who give a special warning that thyroid must not be administered to obese children. Thyroid substance ranks high among the limited number of hormones that are therapeutically orally active. It is true that a large number of the obese, on the basis of their configuration, fat distribution, measurements and other clinical and laboratory findings, are classifiable into certain endocrine groups including the pure thyroid or pituitary or gonadal or combined types and occasionally the true Froelich or Dercum or Cushing syndrome, with or without thalamic or adrenal disease. In fact the underlying endocrine disturbances after adolescence merely determine the type of fat distribution and from a practical standpoint, with the exception of thyroid substance and occasionally gonadotropic factors, when specifically indicated, the use of other endocrines by mouth or by injection for the purpose of weight reduction are not only without value but often harmful. I have seen two women develop a

frank diabetic state under the influence of continued injections of anterior pituitary extract, as a result of the diabetogenic factors in this hormone. The obesity in the post-adolescent state is practically entirely on a basis of increased energy intake or deficient energy output or both with or without water and/or salt retention. Rational treatment must, as already outlined, be based on these facts. In the pre-adolescent, however, an exact evaluation of the endocrine status is of value because much can be done to modify the measurements, the growth, the hypogenitalism, including those with hirsutism or delayed secondary sex characteristics. It is important in the pre-adolescent to remember that with rare exceptions, endocrine treatment be confined to stimulation rather than substitution therapy. Substitution therapy, while justified in later life, should be avoided in the young because of the danger of inducing premature maturation with epiphyseal closure and stunted growth and more important the sparing of already constitutionally deficient glandular function whose idleness is thereby further encouraged, resulting in irreversible deficiency in adult life. A possible exception to this rule is the presence of markedly undeveloped testicles with failure of descent, where the use of gonadotropic hormone is justified; but even in these instances one is often rewarded by a correction of the condition by first trying stimulation therapy. It is here that thyroid substance alone, to the point of tolerance, by its stimulation of the pituitary with secondary gonadal activation often results in gratifying correction of the abnormal fat distribution, increase in growth, testicular development and descent, appearance of secondary sex characteristics, normal genital development and of equal importance an improvement in morale and personality factors and their favorable effect on the schoolwork and social adjustment.

F. Results of Treatment: The immediate results on the actual weight loss and disappearance of troublesome symptoms is not difficult of accomplishment on the basis of the program outlined.

The rate of weight loss which is methodical and safe can be seen in Table 4. Thus, the average weight loss in the female group was 11.3 pounds in 30 days and 24.1 pounds in 90 days, which is equivalent to a loss of 13.2 percent of the total weight, or 51.1 percent of the excess weight above normal. The males show a somewhat better result, averaging 11.4 pounds in 30 days, 28.0 pounds in 90 days or 14.8 percent of the original total weight and 64.0 percent of the excess weight above normal. While the rate of weight loss gradually diminishes after 90 days, it can be stated that 82 percent of the entire group reached a normal level or a figure within 10 percent of it, after a total average period of 8 months. There was no objectionable sagging or wrinkling of the face and neck and in fact with improvement in the general metabolism and nutrition, the skin in most cases showed better tone. The flabbiness of the arms and hips which was sometimes seen in the overconscientious from too rapid initial loss, gradually disappeared with the increased

muscular and circulatory reserve which in themselves increased the physical activity and energy output. Practically all of the patients maintained the weight loss. Many of them have been observed periodically for 2 years after the attainment of a satisfactory level. The maintenance of optimum weight is not a difficult matter, provided the patient at the outset of the program is effectively indoctrinated with the principles involved, according to the program previously outlined.

TABLE IV
WEIGHT LOSS

	30 Days Lbs.	% Days Lbs.	90 Days % Total Weight	% Excess Weight Above Ideal Weight
Female - - - -	11.3	24.1	13.2	54.1
Male - - - -	11.4	28.0	14.8	64.0

Very early in the treatment, the subjects report a disappearance of dyspnea on mild effort, a gratifying loss of fatigue with increased energy reserve and marked improvement in well being. This results from both the initial weight loss and the favorable effect on the mood by the d-desoxyephedrine hydrochloride. With further weight loss and correction of the nutritional status, there is an improvement or disappearance of the symptoms referable to the musculo-skeletal and joint disturbances. The ankle edema gradually disappears. The blood pressure in the essential hypertensives gradually returns to normal levels, while those with hypertensive cardio-vascular disease show some reduction particularly in the systolic level, alleviation of headache and head noises and practically always an increase in the myocardial reserve. The alleviation or more often the complete disappearance of the digestive disorders results from the improvement in liver function together with more rational diet habits, regularity, and the abstinence from condiments, fats, fried foods, and other specific food intolerances. A very gratifying response is seen in the dermatologic group. Those with diabetic xanthoma of the legs and the two cases of indolent necrobiotica lipoidica diabeticorum cleared up completely with insulin. The remaining five diabetics, all of whom were more than 38 percent overweight, reverted to normal carbohydrate metabolism on attaining normal weight, without the use of insulin. Obese diabetics, not included in this series, who showed diabetic retinopathy or impending acidosis were started with insulin and it was necessary to reduce the unit dosage parallel with the rate of weight loss. Most of these cases, provided they were more than 30 percent overweight, acquired normal carbohydrate metabolism without the need of insulin after attaining a normal weight level.

CONCLUSIONS

The results of a statistical study and analysis of symptoms, diagnosis, metabolic abnormalities and sex differences, as carried out on 110 office cases chosen consecutively from the records, have been tabulated and discussed. In all of these cases obesity was a co-

incidental finding and not a specific complaint.

The symptoms in order of their frequency were: fatigue 74 percent, nervousness 59 percent, digestive disorders 38 percent, muscle and joint disorders 35 percent, headache 30 percent, irritability 29 percent, dyspnea on mild effort 20 percent, and so on.

The diagnoses according to the frequency with which they appeared on the records were: menopause syndrome 55 percent, biliary tract disease 42 percent, clinical hypothyroidism 35 percent, cardio-vascular disease 33 percent, musculo-skeletal and arthritic disease 33 percent, nutritional deficiency 26 percent, anxiety and psychoneurotic states 21 percent, endocrinopathy 18 percent, dermatologic disease 17 percent, and so on. The significantly decreased frequency of these conditions in a similarly chosen consecutive non-obese group is emphasized.

The obese group as a whole show abnormal glucose metabolism which is more common in the females. In both sexes, rapid tolerance curves occur about four times as frequently as do the pre-diabetic and frank diabetic curves.

Fifty percent of the female subjects show impaired renal function compared to 21 percent of the males. The females, without exception, and the majority of the males, show chloride and urea excretion levels below average low normal, the means in the female being much lower than in the males.

Hypercholesteremia at levels above 200 mg., was present in 70 percent of the females as compared to 52 percent in the males.

The B.M.R. was below minus twelve percent in 50% of the entire group and averaged the same in both sexes.

Uric acid levels above 3 mg. percent occurred in 49 percent of the males as compared with only 21 percent of the females.

The blood picture showed significantly low blood counts in 52 percent of the females (50 percent microcytic hypochromic, 2 percent macrocytic hyperchromic) while 100 percent of the males had counts well within the limits of normal.

A rational and successful method of treatment is outlined. It is emphasized that there can be no set routine and that treatment must be individualized according to the specific indications based on thorough clinical, metabolic and laboratory surveys including an analysis of the endowed constitutional factors and the personality. The majority of the symptoms and objective findings depend either entirely or in part on the correction of the obesity. Indicated measures including psychotherapy, specific measures, drug therapy, diet, exercise and endocrine therapy are discussed in detail. The psychotherapeutic technic is outlined and attention is called to the importance of correcting the so-called social anxiety, particularly in the younger group. The diet outlined is simple, flexible and imposes no hardship. The employment of exercise for the purpose of increasing energy output and the limitations of exercise are discussed.

Attention is directed to the value of certain cephalotropic drugs and the method of employing them is described. It is concluded from this study on a comparative basis, with other forms of amphetamine, that the drug of choice is d-Desoxyephedrine hydrochloride because it is capable of producing the same central effect with slightly over half the dose required with amphetamine, that the central effect is more prolonged and the undesirable peripheral effects are significantly minimized or entirely absent. In no instance did the drug cause any demonstrable elevation of blood pressure and the group with essential hypertension showed a reduction in pressure parallel with the weight reduction. All of the patients with essential hypertension who were at least 25 percent overweight attained blood pressure levels within normal limits when the weight was reduced to a normal level. It can be concluded from this study that d-Desoxyephedrine is definitely not contraindicated in essential hypertension when it is used in the dosage and manner outlined. In patients with hypertensive cardiovascular disease manifesting coronary artery insufficiency or disease with or without hypertensive retinopathy, nephropathy or encephalopathy, the drug must be used with great caution or not at all.

Endocrine therapy is discussed, and it is pointed out that thyroid substance should not be employed except when indicated by the presence of definitely demonstrable clinical evidence of hypothyroidism. The presence of a low B.M.R. in itself is not an indication for thyroid administration. Attention is directed to the value of thyroid substance in the preadolescent group; the importance of stimulation rather than substitution therapy in certain conditions is discussed. Injections, except in unusual cases when specifically indicated, are of no value. Routine use of anterior pituitary extract is dangerous. Injections of iron are without value (13). It is much more effective orally. The continuous periodic and routine injections of estrogens in natural or synthetic form are not only unnecessary but often harmful and potentially dangerous. Here, also, oral administration in the smallest doses necessary to control the symptoms is more rational, cheaper and safer.

The favorable results in the alleviation of symptoms and the correction of the metabolic and dynamic abnormalities, together with data on the rate of weight loss, are discussed in detail.

It is emphasized that in order to obtain the cooperation of the patient and to successfully attain results which are lasting, the subject must be thoroughly indoctrinated with the underlying principles involved, the relationship of the abnormal metabolic findings and disturbed circulatory and musculo-skeletal dynamics to his obesity, a simple explanation of the dietetic principles and the goal to be achieved. This takes a little time, but without it, successful and lasting results, particularly in the intellectual group, are more often not attainable.

Finally, it can be stated that on the basis of statistical analysis, the incidence of metabolic, functional, ana-

tomic and nutritional abnormalities in the obese is so definitely greater than in the non-obese as to place the

correction of this condition among the most important categories of preventive medicine.*

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Report of a Case of Spontaneous Cholecystoduodenostomy

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RECENTLY, we encountered a very interesting and unusual roentgen finding in the course of a routine gastro-intestinal examination. Following is a report of this case.

The patient, a sixty-eight year old white female, was referred to our department on July 8, 1946, for a gastro-intestinal examination because of a long-standing history of pernicious anemia. She had no complaints referable to the gastro-intestinal tract at the time of this examination.

Study of the stomach and duodenum with contrast media did not reveal any intrinsic pathology. However, arising from the apex of the duodenal cap, the gallbladder, cystic duct, common hepatic duct, left and right hepatic ducts, and common bile duct, were all well-outlined with barium. The gastro-intestinal examination was repeated on August 14, 1946, with the same findings as above. Questioning of the patient revealed no history of any operative procedure but she had been admitted to this hospital on two previous occasions.

On February 20, 1943, the patient was admitted to the Buffalo General Hospital because of persistent,

severe pain for five days in the right upper quadrant of the abdomen which radiated to both costal margins and into the interscapular area. In addition, she complained of constipation for the two weeks preceding admission with no bowel movement during the four days preceding admission. There was no history of nausea, vomiting, chills, fever, or jaundice. A gastro-intestinal examination was done in this department. No abnormalities were noted. This was followed by a gallbladder dye series which showed a non-functioning gallbladder with one calcified stone shadow, one-quarter of an inch in diameter, in the gallbladder area.

The patient improved rapidly under symptomatic treatment and she was discharged from the hospital, symptom-free, on March 13, 1943.

The patient had no more complaints referable to the above illness until July 12, 1943. At that time, she began to have pain in the right upper quadrant of the abdomen which radiated around to the back and into the interscapular area. This was accompanied by nausea, emesis, and obstipation. These complaints continued up until admission to the hospital on July 21, 1943. There was no history of jaundice or of light-colored stools.

Examination upon admission revealed some tenderness in the right upper quadrant of the abdomen. Otherwise, there were no findings referable to the above complaints.

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The patient did have a mild leucocytosis and an icteric index of 15-20.

A gastro-intestinal examination with contrast media was done in this department but no abnormalities were demonstrated. The calcified stone shadow noted previously in the right upper quadrant of the abdomen was no longer present.

The patient became symptom-free on a fat-free diet and bed rest. She was discharged on August 8, 1943, with no complaints.

In reviewing the patient's history, it would seem most probable that the gallstone noted at the time of the first admission to the hospital eroded through the fundus of

the gallbladder into the duodenum. This apparently occurred during the nine days preceding the second admission to the hospital. The gallbladder apparently remained attached to the duodenum, forming the permanent cholecystoduodenostomy which we demonstrated in the examination of July 8, 1946.

There have been several cases reported in the literature of spontaneous rupture of the gallbladder allowing stones to pass into the stomach and duodenum, and even into the colon, with formation of permanent fistulae. This has also occurred from a stone in the common duct rupturing into the duodenum. Such permanent fistulae may also be formed by retrograde lesions, such as a duodenal ulcer or colon malignancy becoming adherent to the gallbladder and eroding the gallbladder wall. These lesions may go unsuspected until roentgen studies of the gastro-intestinal tract with contrast media reveal the abnormal communication.

Borman and Rigler exhaustively reviewed the literature on spontaneous internal biliary fistulae in 1937, and presented three cases diagnosed by roentgen examination. According to the above authors, the most common cause of a spontaneous internal biliary fistula is a gallstone eroding through the gallbladder wall into another hollow viscus. The most common site of erosion is into the duodenum, and less commonly, into the stomach or other viscera.

Weinberger and Rosenthal presented a case of a spontaneous choledcho-duodenostomy from a duodenal ulcer eroding into the common duct.

Slinger described a case of spontaneous cholecystogastrostomy from a gallstone eroding into the stomach.

Pomeranz, Grady, Peelen, and Magnes reported a case of spontaneous cholecysto-duodenostomy in a patient with a primary hepatoma of the liver.

The diagnosis of these lesions has become more commonplace with the advent of better methods of roentgen examination of the gastro-intestinal tract. Without roentgen examination, the diagnosis of spontaneous internal biliary fistula is seldom made.



Fig. 1.—Film of the stomach and duodenum showing the fistula between the duodenal bulb and the gallbladder which allowed barium to enter and visualize the biliary tract.

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Diabetes Mellitus Complicated by Addison's Disease; Case Report with a Review of the Literature.*

By

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BLOOMFIELD (1), IN HIS review of the literature and case report has pointed out the rarity of Addison's disease and diabetes mellitus co-existing in the same patient. Since the publication of his paper, several other similar cases have been recorded in the medical journals with a number of interesting observations which are summarized herein. In addition, another well authenticated case of this infrequent combination is reported.

The physiological antagonism between the secretions of the suprarenal cortex and the Islands of Langerhans is well recognized, and it is emphasized by the almost universal hypersensitiveness to insulin observed in diabetics suffering from Addison's disease. It is paradoxical that diabetes should develop at all in the presence of adrenal cortical insufficiency, and a critical survey of the literature confirms, as Thorn and Clinton first pointed out (12), that diabetes is the antecedent disease in all except three instances of both endocrine disturbances in the same patients.

The normal antagonism between the adrenal cortex and the Islands of Langerhans is well demonstrated in the accompanying case report by the occurrence of reciprocal exacerbations of one disease associated with remissions of the other.

REVIEW OF THE LITERATURE

Only nineteen proven cases of diabetes mellitus and Addison's disease occurring in the same individual are recorded in the medical archives (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14, 15, 16). One of these (2) was produced surgically by bilateral denervation of the adrenal glands in an attempt to relieve pre-existing diabetes, with the eventual death of the patient from Addison's disease. Besides the rarity of this combination, the outstanding clinical feature which these patients exhibit is a hypersensitivity to insulin. In fourteen of the nineteen cases this characteristic was definitely noted, while in the remainder the tolerance to insulin was not reported. Thorn and Clinton (12) warn especially against the use of protamine zinc insulin, and suggest, not unreasonably, that the low blood sugar characteristic of Addison's disease, may not be due directly to deficiency of adrenal cortical hormone. In nine of the cases diabetes was the original disease, and in three cases Addison's diabetes occurred first. The administration of adrenal cortex seemed to precipitate the diabetes in Levy-Simpson's patient (5). In

two cases (1, 13) the patients seemed to respond somewhat differently to desoxycorticosterone acetate than to adrenal cortical extract. When the former was used, the sensitivity to insulin became less acute and the severity of the diabetes increased. In two diabetics (16) a sensitivity to insulin was noted before the clinical onset of Addison's disease.

CASE REPORT

The patient was admitted to the Milwaukee County General Hospital October 17, 1939, complaining of vomiting and severe generalized asthenia of three weeks' duration. Until the onset of the present illness she had been in good health except for diabetes mellitus which in the course of the previous twelve months had become less and less severe. About four months previously, however, she became aware of the development of a number of dark brown spots on the skin, and her friends began to remark to her of the dusky hue which her complexion had acquired. She had been a patient in the Diabetic Clinic of the Milwaukee County Dispensary since September, 1938. From then until her admission to the hospital, her dosage of protamine insulin had been reduced from 30 to 10 units daily, while the blood sugar during the same period fell from 333 mgm. per cent to 167 mgm. per cent. Moreover, she not only often omitted taking insulin, but also completely disregarded all diabetic dietary regulations, eating just about whatever she pleased. From the time of onset of her immediate symptoms, she received no insulin until October 14, when she took 15 units.

Past history revealed the development of a non-toxic thyroid adenoma in 1928 which never required treatment. In 1935 a subtotal hysterectomy and a right salpingo-oophorectomy was performed because of a uterine fibroid with hemorrhage and the presence of a cyst in the right ovary. Diabetes mellitus was first diagnosed in January 1936. The disease at first was mild and was readily controlled with regular insulin 5-0-5, but it gradually increased in severity until the time of her admission to the Diabetic Clinic of the Milwaukee County Dispensary.

The family history was negative for tuberculosis and cancer. A sister and a niece of the patient, however, were severe diabetics.

Physical examination at the time of admission revealed a 28 year old white female, poorly nourished and acutely ill. The pulse was weak and the rate 100. The blood pressure was 84/62. The skin was uniformly bronzed and several diffusely scattered deeply pigmented spots were noted. An adenomatous mass was palpable

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in the thyroid isthmus. The heart tones were weak in quality. No other significant physical findings were present.

On laboratory examination the urine was sugar free and the blood sugar was 67.8 mgm. per cent. Blood chlorides were 400 mgm. per cent and urine chlorides 100 mgm. per cent. The blood picture, except for a slight lymphocytosis, was normal. An intracutaneous test with old tuberculin 1:1000 was negative, and a roentgenogram of the chest was normal.

On a basis of this clinical picture a diagnosis of Addison's disease in the stage of crisis was made and immediate treatment with cortin, sodium chloride and glucose instituted with a very satisfactory clinical response. The asthenia and gastro-intestinal symptoms disappeared, her appetite returned and she regained weight, strength and vigor. After two weeks of treatment, however, she developed a heavy glycosuria with a hyperglycemia of 204 mgm. per cent, but no signs of acidosis. Improvement continued until November 10, when she was discharged on a dosage of 10 cc. of cortin every other day, a sodium chloride intake of 20 gm. daily, and no insulin or other dietary regulations.

The patient was readmitted on November 25, 1939 in another moderately severe Addisonian crisis, although she manifested a mild hyperglycemia and a moderate glycosuria. Again she responded well to increases in the amount of cortin and sodium chloride, but the glycosuria and hyperglycemia became more severe, and on December 3, administration of regular insulin 25-0-0 was begun. On December 10, a change to protamine insulin 30-0-0 was made with immediate appreciable effect on the amount of sugar in the blood and urine. Five days later, however, an insulin reaction occurred, prompting a reduction in protamine insulin to 20 units daily. Paradoxically, with the reduced dosage, both the hyperglycemia and the glycosuria improved, the patient felt definitely better, and further reduction of the daily insulin dosage to 10 units accentuated this

beneficial turn in the condition of the patient. She continued to feel well until January 1, 1940, when she complained of anorexia and refused her insulin. Blood chemistry determinations revealed the development of an azotemia and a carbon dioxide combining power of 49 vol. per cent. On January 3rd she became comatose, had a tonic convulsion with carpopedal spasms and expired two days later without regaining consciousness, despite the administration in heroic doses of cortin, sodium chloride and glucose.

Post mortem examination performed by Dr. L. J. Van Hecke revealed in substance the following pathological changes. The normal adrenal tissue was revealed by soft fibrous tissue bilaterally, and only a vague suggestion of the normal color of the adrenals was apparent. Microscopically the glands had undergone complete fibrosis and atrophy. The pancreas showed fibrosis and a decrease in the number of islet cells. The skin showed atrophy and increased pigmentation of the stratum germinativum. Permission for examination of the abdomen only was obtained.

SUMMARY AND CONCLUSIONS

1. Diabetes mellitus complicated by Addison's disease is a clinical rarity; Addison's disease complicated by diabetes is even more so. Only twenty cases, including the one herein reported, are to be found in the medical literature.
2. When this combination exists, a hypersensitivity to insulin usually is found also.
3. The hypoglycemia and high glucose tolerance characteristic of Addison's disease are probably due to some more immediate factor than a deficiency of adrenal cortical hormone.
4. Sensitivity to insulin is less pronounced when desoxycorticosterone acetate is employed in the therapy of Addison's disease, and under the same circumstances the diabetes may be more severe.

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New Hemostatic Agents in Proctology

By

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INTRODUCTION

THE PROCTOLOGIST, operating in an extremely vascular field, requires careful hemostasis not only to prevent excessive blood loss at the time of surgery but also to eliminate the possibility of post-operative blood loss. This is particularly important if the proctologist proposes to perform his surgery in ambulatory fashion. It is obvious of course, that all proctologic patients, whether hospitalized or ambulatory, must be given the benefit of adequate hemostasis during surgery. For the ambulatory patient, however, such hemostasis is of especial importance. Post-operative hemorrhage should never occur in proctologic surgery. To prevent such post-operative hemorrhage it has been necessary to utilize every possible means at our disposal.

The primary technique required, of course, is a careful surgical hemostatic method. All bleeding points are carefully clamped and ligated. In performing a hemorrhoidectomy, for example, the first step is to insert a hemostatic suture-ligature through the base of the pile pedicle. This controls bleeding from the major hemorrhoidal vessels. If an electro-surgical technique is used it is usually best to underlie the area of proposed eschar by sutures. Usually this is in the form of a running suture from the pile pedicle to the skin surface. This is done so that the eschar, when separating, will be reinforced by the underlying suture, thus preventing blood loss at the time of such separation. If an open technique of hemorrhoidectomy is employed, without electro-surgical cauterization, ligation of each bleeding point becomes exceedingly important. These bleeding points are particularly evident along the cut margins of mucosa and skin. Each is clamped with a mosquito clamp and carefully ligated with plain 1 cat-gut.

As further insurance against bleeding various hemostatic agents have been developed during the past several years, and these agents have been carefully evaluated in their proctologic application. We first attempted to employ thrombin in topical fashion and utilized it as follows: after the completion of the surgery the thrombin was drawn into a syringe and was sprayed over the wound surfaces, the excess thrombin being caught upon a gauze wick. This gauze wick was then further saturated with thrombin and inserted into the anal orifice as high as the upper level of surgery. At a later time we employed fibrin foam with thrombin, and still later we attempted the use of the gelatin sponge saturated with thrombin solution. Our present series involves the use of oxidized cellulose, without thrombin.

It is the purpose of this paper to evaluate these

new hemostatic agents in their application to proctologic surgery.

NEW HEMOSTATIC AGENTS

As has been stated, there can be no substitute for careful surgical technique. However, assuming that the surgical technique has been careful and the hemostasis meticulous, the field of application for the new hemostatic agents is still great.

Topical thrombin, as prepared by Parke, Davis and Company, is presented to the profession as a powder, soluble readily in either water or normal saline solution, producing an opalescent solution. It has been our policy to prepare this thrombin at the time of operation. If desired, however, it is possible to maintain the activity of the solution for several days if it is kept well refrigerated. It is my impression, however, that it is better to prepare the solution immediately at the completion of surgery and to apply it at that time.

Each ampoule of topical thrombin contains approximately 10,000 thrombin units. The thrombin unit is said to be that amount required to clot 1 cc. of standard fibrinogen solution in 15 seconds. The ampoule containing the white thrombin powder is sterilized and opened. Ten cc. of sterile water is then drawn into a syringe from another ampoule and this water is then forcibly ejected into the thrombin powder. The thrombin dissolves immediately and completely. The resulting concentration is approximately 1,000 units per cc. Such concentration will produce clotting of an equal volume of human blood in a period of less than one second, and will clot 10 times that volume within a 3-second period.

This thrombin solution is applied to the bleeding surfaces, or to the surfaces of surgical excision, by means of a syringe and needle. The solution is not injected, but is merely sprayed over the surfaces. A gauze wick is held at a dependent position beneath the anal orifice to catch any excess thrombin solution as it drips from the sprayed surfaces. The wick is then saturated more thoroughly and is inserted into the anal canal. As a further precaution two or three cc. of the thrombin solution can be injected directly into the anal canal. For this purpose the needle is removed from the syringe and the tip of the syringe is inserted gently into the anal orifice, thus allowing the solution to be forcibly ejected into the canal. This is best done after the wick is in place so that it will further absorb the injected thrombin solution.

The wounds must be relatively free from blood at the time the thrombin solution is applied. There is little point in merely clotting the surface layers and permitting bleeding to continue beneath this clot. The hemostatic clot produced must be left in place. Thus, sponging must be avoided after the thrombin has been utilized. If the clot is sponged bleeding usually re-

sumes. We have not attempted application of the dry thrombin powder, although this is said to be equally effective.

There has been no evidence of local irritation or infection produced by the use of thrombin. The wounds healed promptly and without evidence of irritation. Thrombin may thus be said to be an adequate hemostatic agent, and until the time of the development and application of oxidized cellulose we considered it to be the best of the hemostatic agents.

The large scale fractionation of blood plasma has recently made possible the development of a new hemostatic agent. This hemostatic agent is composed of the human proteins involved in the natural blood clotting mechanism. Two forms of this material, known as fibrin foam, have been studied. In one form the fibrin foam contains very little thrombin, and is to be used with a separately packaged thrombin preparation. The other form already has the thrombin intrinsically combined. The separately packaged fibrin foam and separately packaged thrombin have been extensively applied clinically.

The fibrin foam is thus made available as a non-irritating sponge to be moistened with thrombin solution and to be applied to the bleeding surface. The sponge is left in place. The fibrin foam thus acts more or less as a "human" surgical sponge, and over this matrix the blood clot forms. The thrombin with which the sponge is saturated, of course, simply facilitates the normal coagulation of blood.

It might be wise to here review briefly the mechanism of blood clotting. Thromboplastin is released when cell injury occurs. The normal plasma protein known as prothrombin, together with calcium, combines with thromboplastin to form thrombin. The thrombin thus produced combines with fibrinogen, another plasma protein, and produces fibrin. This fibrin is the basic structural material of the blood clot.

During the process of blood fractionation fibrinogen is separated from plasma. This fibrinogen is combined with thrombin, is whipped to a spongy mass, and is quick frozen and vacuum dried to produce the light, brittle sponge known as fibrin foam. When this sponge is moistened with the thrombin solution it becomes pliable, soft, and is readily molded to the bleeding surface. It should be noted that the material employed in the production of fibrin foam sponges is entirely homologous, non-reactive human protein, a completely natural substance. It is thus non-irritating, absorbable, and can be left in place without danger of disturbing or delaying healing appreciably.

In practical application in proctologic techniques the use of fibrin foam is not completely satisfactory. The hemostatic action is entirely adequate, but the difficulties involved in the preparation of the fibrin foam sponge are not adequately compensated for by increased hemostatic action over that produced by thrombin alone. The same may be said for the gelatin sponge.

The gelatin sponge is utilized in approximately the same manner. The sponge is soaked in the thrombin

solution, is then pressed dry to express the air within its meshes, and is now once more soaked in the thrombin solution. This sponge is then applied to the surface of the bleeding wound. Again, the complexity of preparation is not compensated for by any increased hemostatic action. It must not be thought that the author is condemning either of these agents for their inadequacy as hemostatic materials. They are entirely adequate. It is merely to be understood that in proctologic surgery simplicity of technique is most desirable, and these more complex agents need not be employed.

We come now to the consideration of oxidized cellulose. Oxidized cellulose is supplied by Parke, Davis and Company, as individual sterile pads (Oxycel). These pads are prepared from gauze by a special oxidation process. This process converts the unoxidized cellulose into polyanhydroglucuronic acid, and this acid is absorbable and hemostatic. This oxidized material cannot be repeatedly autoclaved, and should be used at the time the package is opened.

In contact with blood the oxidized cellulose becomes brownish-black and gelatinous. Bleeding usually ceases when this brownish-black discoloration occurs.

The technique of application is exceedingly simple. The oxidized cellulose is applied directly to the oozing surface. Pressure can be made over the Oxycel by means of a gauze tampon. Usually, however, this pressure is not necessary, and the Oxycel stops the bleeding by itself. The use of pressure and a reinforcing tampon is usually necessary only in the presence of brisk bleeding. Such bleeding, however, is best corrected by clamp and ligature.

The oxidized cellulose may be employed as a carrier for topical thrombin. However, inasmuch as the oxidized cellulose is of acid character it is incompatible with thrombin, and must first be neutralized with a sterile solution of 1% sodium bicarbonate. The technique for this application will not be detailed here inasmuch as it is not necessary to utilize the thrombin in proctologic surgery. We prefer to use the oxidized cellulose without topical thrombin.

Oxidized cellulose seems to owe its hemostatic quality to the formation of a coagulum consisting of salts of polyanhydroglucuronic acid and hemoglobin. A further factor is the swelling of the material itself when moist, thus producing a pressure packing.

Our technique for the use of this material in proctology is simply to introduce the strip of oxidized cellulose directly into the anal canal. Thus it acts both as a pressure packing and as a direct hemostatic agent. Of course meticulous hemostasis has already been accomplished before the Oxycel is introduced. All bleeding points have been carefully clamped and ligated. No oozing of blood is seen at the time of introduction of the oxidized cellulose. Thus the material does not turn brownish-black at this time. It will only do so in the presence of free blood. This property of color-change gives it a diagnostic as well as a hemostatic value. Should free bleeding occur at any subsequent time the oxidized cellulose becomes a brownish-black color, thus

serving as an indicator of internal bleeding.

Oxidized cellulose provides an excellent post-operative dressing in open pilonidal wounds. It is spread over the inner surface of the wound and ordinary gauze is then packed on top of this lining. A pressure dressing thus applied immediately stops all minute capillary ooze. Oxidized cellulose is also especially valuable in the handling of oozing from tattoo-neurotomy wounds. In the procedure of tattoo-neurotomy an extensive area of skin in the perianal region is undercut, and the oozing from the four incisions is sometimes extensive. Oxidized cellulose, when applied directly to the incision areas, usually controls this ooze very rapidly. It is necessary in this instance to make pressure over the oxidized cellulose with ordinary gauze sponges. The oxidized cellulose turns brownish-black in contact with the free blood, and a firm clot is thus formed. The Oxycel is not removed, but remains in place as part of the dressing.

Within a period of twenty-four hours from the time of application of the oxidized cellulose the material undergoes rather extensive changes. It becomes very soft, very friable, and cannot be removed intact. Indeed, there is not need for such removal. Whether the material is used as a packing after hemorrhoidectomy or fistulectomy, the gauze can be left in place. It rapidly becomes friable and soft and more or less falls away from the wound within the first few days. When used as a packing after hemorrhoidectomy or prolapse surgery the protruding outer portion of the oxidized gauze wick can be removed. No attempt need be made to remove that portion which shreds off in the process and remains behind within the anal canal. This does not act as an avenue of infection, or as a source of irritation. Furthermore, it facilitates hemostasis during the

next day, and is passed with the first bowel movement.

Thus, in every fashion, the ease of application of oxidized cellulose, its freedom from irritating action, and its remarkable hemostatic qualities, render it an ideal hemostatic agent for proctologic surgery. Oxidized cellulose is now employed routinely in all our proctologic surgical procedures.

Of the hemostatic agents above described it is our impression that oxidized cellulose offers the greatest number of advantages. It cannot substitute, it must once again be emphasized, for meticulous surgical hemostasis. It is assumed that the surgical technique will be adequate. Assuming this, however, as an additional safeguard against post-operative bleeding the employment of oxidized cellulose offers many advantages and no discernible disadvantages.

The question is often asked what percentage of post-operative hemorrhage occurs in the ambulant proctologic surgical case. If the surgical technique is adequate hemorrhage need not occur even if these new hemostatic agents are not applied. It is rare to see such hemorrhage either in the ambulatory patient or in the hospital proctologic problem. With the additional advantage of these newer hemostatic agents such post-operative bleeding should become rarer still.

CONCLUSIONS

1. Adequate surgical technique with meticulous hemostasis is the primary requisite to safeguard against post-operative hemorrhage in proctologic surgery.
2. The newer hemostatic agents are described, including topical thrombin, fibrin foam with thrombin, the gelatin sponge with thrombin, and oxidized cellulose.
3. Oxidized cellulose appears to be the agent of choice in proctologic surgery.

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Azotemia in Gastro-Intestinal Hemorrhage.

By

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THE problem connected with the occurrence of azotemia after gastro-intestinal (g. i) hemorrhage, has during the later years been discussed in medical circles the world over. Since this phenomenon was first pointed out by *Sanguinetti* (1) in 1934, several clinicians in Scandinavia and Holland have contributed to the discussion, amongst them *Christiansen* (2), *Meyler* (3), *Clausen* (4), *Alsted* (5), *Schrumpf* (6), *Kobro* (7), *Borst* (8), and *Guldager* (9). Since this problem has attracted the interest of several colleagues in U.S.A. as well (*Kaump & Parson*, *Black & Lesse*, *Schiff* and collaborators) it may be useful to give a short resume of the opinions set forth by Scandinavian and Dutch clinicians.

To begin with it is necessary to point out that the azotemia can be observed *initially* after the bleeding, or *late*ly, often after the bleeding has stopped. This does not exclude the possibility that both types of azotemia can appear in the same patient, the one following more or less closely after the other. The late azotemia, which often ends fatally if not diagnosed, was first described in Scandinavia by *Mossberg* (10). in 1933, but this author did not recognize the true nature of uremia which dominates the picture. Other authors have contributed to our knowledge of the condition, such as *Christiansen* (2), *Meyler* (3), *Hesser* (11), *Schrumpf* (6), *Ustvedt* (12), *Kobro* (7), in Scandinavia and Holland. It is now fully understood, that this late form of azotemia after g.i. hemorrhage is caused by dehydration and increasing circulatory failure, which impairs kidney function.

But how is the azotemia to be explained which can be observed during the first week after g.i. hemorrhage? Several theories and clinical observations have been put forward to solve the question. *Christiansen* suggested that the rise of blood urea was due to disturbances of the chloride metabolism. Toxic factors in connection with paralytic ileus are considered as a possible cause by *Kobro* (7), *Meyler* (3) has drawn our attention to troubled water metabolism, while *Christiansen* (2) and *Kobro* (7) suppose liver insufficiency to be a contributing factor. The close relationship between the azotemia and the digestion of blood in the intestine has been pointed out by several authors such as *Sanguinetti*, *Borst*, *Christiansen* and *Guldager*. *Meyler* and *Schrumpf* stated that increased protein catabolism is the chief cause of the azotemia, while *Borst* and *Christiansen* suggest that hemodynamic factors in connection with impaired kidney function may give a possible explanation. *Kaump & Parsons* (13) in U.S.A. state from experiments on dogs that

the blood urea rise was due to assimilation of the ingested protein and digestion products of the whole blood in the g.i. tract and an increase in protein catabolism. As will be learned from this brief summary, the problem connected with the initial azotemia seems far from solved.

It may therefore be of interest to point out some features of importance, partly based on own investigations: (1) First of all this azotemia after g.i. hemorrhage is of frequent occurrence. In my own material of 55 cases it was observed in 43 instances. The peak of azotemia is generally reached during the first 3 days and normal blood urea is restored during the last days of the first week, or the first days of the second week.

(2) An important factor which must be taken into consideration is the nutritive state of the patient and the qualitative and caloric value of the diet during treatment. Many investigators seem to have neglected this point, in spite of the reasonable physiologic fact, that a negative nitrogen balance will cause an increased endogenous protein destruction and subsequent rise of blood urea. In fact I have been able to demonstrate, that negative nitrogen metabolism and azotemia may be found during the common dietetic treatment of *non-bleeding ulcers* as well. The common treatment of bleeding ulcers is qualitatively and quantitatively insufficient, so that—to a certain degree—conditions are established similar to the metabolism during hunger. In fact the azotemia appears at a time when the negative nitrogen metabolism is most pronounced.

(3) Experiments have proved beyond doubt, that absorption of blood in the intestines can give rise to blood urea increase. This has clearly been demonstrated by *Clausen*, *Kobro*, *Schrumpf* and in U.S.A. by *Schiff* (14) and co-workers. The rise of blood urea however, after experimental blood feeding is not very pronounced and reaches its maximum during the first 24 hours (in my own investigation after 4 hours). This rise seems to be chiefly due to other nitrogenous components (amino acids?) rather than urea in my own investigations, and is therefore basically different from the blood urea rise after g.i. hemorrhage.

(4) Since *Taylor* and *Lewis* (15) in 1915 could demonstrate the fact in dog experiments that repeated loss of blood with restoration of fluid loss by saline, was accompanied by rise of rest-N, it may be supposed that anemia influences the azotemia. No such correspondence could however be registered in my own investigations, even in cases of severe hemorrhage.

(5) Much work has been done to examine the role of fluid and salt metabolism after g.i. hemorrhage. The question is a rather complicated one. It must be kept

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in mind that isolated determination of chloride in blood and urine is not conclusive as to water metabolism. It is only on behalf of base balances in connection with weight determination that such conclusions may be drawn. The general treatment of g.i. hemorrhage is apt to inflict a marked negative base balance, in my own material most pronounced during the fifth day. Only in one of 6 cases could a drop in serum base be demonstrated. No relationship, however, between serum chloride and blood urea or between base balance and azotemia could be traced. It therefore seems rather doubtful in my opinion, that the azotemia after g.i. hemorrhage is related to disturbances in water or salt metabolism. Shock or collapse is practically never observed in patients after delivery into hospital, so these hemodynamic factors may be ruled out. (In the late azotemia, however, oligohydremic collapse is a prominent feature).

(6) As to whether or not the kidneys play a role in the azotemia after massive g.i. hemorrhage, opinion is divided. *Borst* and *Christiansen* ascribe to the kidneys a certain function and *Black* and *Lesse* (16) in U.S.A.

as well. *Guldager* denies it. In a number of cases examined by me, it could be proved beyond doubt that glomerular filtration was normal in all cases of g.i. hemorrhage. This was the case after oral administration of blood as well. Urea excretion determinations were normal too. It could further be proved, that tubular reabsorption, urea excretion percentage and plasmareosorbate-difference were practically normal in all instances as well after g.i. hemorrhage as after oral administration of blood.

From considerations and results mentioned above, it can be concluded that the azotemia after massive hemorrhage in the upper g.i. tract is not caused by one single factor. There can in my opinion be no doubt, that the chief factor is of dietetic origin, as the diet used is insufficient for protein and energy requirements. This again increases protein catabolism and waste of tissue. A second factor is, that the absorption of blood to a certain, but moderate degree can play a part in the development of the initial azotemia. All other factors seem under ordinary conditions to be of little or no importance.

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A Creed for the Treatment of Diabetes

By

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THE pathological physiology of diabetes mellitus is no longer an uncharted sea. The complex mechanism of carbohydrate metabolism in relation to total metabolism of the food-moieties is rapidly being elucidated (1-2-3-4-5-6-7.) Accordingly, there can be no legitimate excuse for premising present-day treatment on less than a solid approach to normal physiology. It must be obvious that without a knowledge of what constitutes normalcy, one cannot successfully appraise variants from the normal much less interpret these diversions in respect to what constitutes "adequate treatment." In this connection, there frequently arises a question which must be pondered: "Is hyperglycaemia with its resultant glycosuria *always* necessarily detrimental to the organism?" The clear

thinker, in relation to modern concepts of physiology, must answer this question in the negative.

If it be admitted, that in the *non-diabetic* under certain conditions, hyperglycaemia may be useful and conservative, it must also be admitted that in the *diabetic* under the same conditions, hyperglycaemia may likewise serve a constructive, conservative, and even corrective function. One may cite the protection afforded by a high blood-sugar concentration to the damaged parenchymal cells (8-9-10-11-12-20) of the liver, the advantage of a promptly available and abundant glycogen in degenerated cardiac muscle (13-14-15-16-17-18-19) especially in the anginal syndrome, the safety insurance of a definitely positive balance of liver glycogen in patients facing surgical crises, the effective diuretic influence of sustained high blood-sugar in the uremic state, the protective influence of maintained glycaemia against rupture (21) of fragile retinal vessels in *advanced* retinitis. In advanced arteriosclerotic retinitis, the counter-part of this state

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of glycaemia, relative or absolute hypoglycaemia, will all too frequently witness prompt impairment of vision incidental to capillary rupture under stress when the so-called normal text-book standards of blood-sugar (21) are insisted on. The elderly *non-diabetic* with arteriosclerosis frequently carries a blood-sugar (22-23-24) level which is definitely higher than arbitrary normal standards; yet he shows no inability whatsoever to utilize sugar normally. "Gild the Lily" in these individuals by attempting artificially to correct such theoretically high blood-sugar (21-25) and watch the victim of such meddle-some therapy be transformed from a relatively normal to a seriously ill individual. Clinical experience suggests that phases of measured high blood-sugar concentration in these particular and exceptional instances are supportive and constructive of well-being, whether or not the individual be diabetic.

It is, however, a far cry from such specific instances of the advantageousness of high blood-sugar to the philosophy of unbridled unmitigated hyperglycaemia and glycosuria in the average uncomplicated diabetic patient or in all diabetics in general. Such *carte blanche* abandon (70-71-72) of well tried and fully established physiologic principle is to be as strongly deprecated as are, at present, the extremes of starvation (26-67) once practiced in the pre-insulin era. Then, laboratory perfection was all too frequently associated with untimely clinical death of the patient despite the over-all improvement in mortality statistics of the day attributable alone to dietary restriction. The starvation regimen as then practiced resulted in extremes of fatty infiltration of the liver with a false picture of improved carbohydrate (27-21) tolerance.

This faulty philosophy of perfect control while the patient died of starvation was much like: "The operation was successful but the patient died." The underlying principle of unburdening (29) the metabolic mechanism was correct; its extreme application, however, defeated its own purpose. The opposite extreme, that of indiscriminate encouragement of unbridled hyperglycaemia, represents in a way an ill founded homeopathy, for persistent hyperglycaemia itself except in rare (30) instances favors progression of the very pathology one should be striving to correct, degeneration of the "end organ" in carbohydrate metabolism, the islets of Langerhans (31-32-33-34). In fact, in the light of recent developments, one must fathom whether treatment in a given case shall be aimed at the preservation of islet tissue or at deliberate sacrifice of the "end organ" to the immediate comfort of the patient and/or the convenience of his medical attendant. The physician in most early cases has at his disposal either modality of treatment. Fortunately, or unfortunately for morbidity, with protamine zinc insulin it is now entirely possible to maintain life and sustain a reasonable sense of well-being without the slightest (35-36) semblance of chemical control. The ability to maintain a positive nitrogenous balance with protamine zinc insulin has made this feat possible in spite of the almost inevitable "bankruptcy" of the patient's own insulin mechanism as a result of the

extravagant insulin wastage. Surely between these extremes of starvation with false chemical control on the one hand and a "glycosuric paradise" with wanton freedom of diet and failing carbohydrate tolerance on the other, there must be some safe and desirable (37) middle-ground, what Peters so aptly calls "a middle ground of contentment."

Clinical diabetes begins in the guise of an excessive demand (38-39-33) on the part of the organism for an increased production of insulin. The inordinate insulin demand puts the insulin mechanism to extremes of over-production (58).^{*} Subsequently there is added to this excessive and fatiguing demand for insulin a decreasing ability on the part of the mechanism to produce even enough insulin to meet ordinary normal demands (38-39) much less the exaggerated requirements; or if the pancreas is still able to produce in considerable quantity, a state of resistance or insensitivity on the part of the organism to insulin supervenes, producing the end result of a relative insulin insufficiency. This was mathematically demonstrated by Himsworth (40) who (figs. I, II) pointed out that insulin effect is less a matter of quantity of insulin than it is a function of the degree of sensitivity of the organism to insulin. As a result of insulin-resistance, both endogenous and exogenous insulin suffer from the law of diminishing returns for a given amount of insulin no longer has the anticipated effect. That sensitivity plays an important role in insulin efficiency is further indicated by the fact that with suitable unburdening and subsequent adequate stimulation of the mechanism by diet a return to normal insulin (40) sensitivity can usually be effected.

One may not disregard these concepts in planning treatment for the average diabetic. While treatment must be individualized (65), the very first step should, of course, be an attempt to reduce the excessive insulin demands. The second step should be an effort to help the individual meet these minimized demands as adequately as is possible. At a later time one should attempt to *stimulate increased "returns" on insulin* (both exogenous and endogenous) or an increased amount of carbohydrate utilized per unit of insulin.

Insulin has come to be recognized as part of a complex enzyme mechanism (1-2-3-4-5-6-7). Its main function is now thought to be an indirect one in relation to carbohydrate metabolism, namely that of inhibiting the anterior hypophysis^{**}. Whatever may be the facts as to the actual mechanism of insulin function, one may never forget one fundamental truth that while insulin may *theoretically* be unnecessary for glucose utilization by the cells, without insulin *normal*

^{*}Soskin refutes the claim (41) that quantitative assay of the pancreas necessarily bespeaks the productivity of that gland. While his point must be admitted from an exact over-all quantitative standpoint, the consistency of the variations under fixed experimental conditions must certainly be more than accidental. Surely they would indicate that at the instant of excision of the specimen there was evidence of paucity or excessive production of insulin. The pancreas is to a considerable extent a storage gland.

^{**}In their work on hexokinase, the Coris (7) have confirmed the principles enunciated by Houssay (44-56-57) and verified by Long (60), Young (58), Dohan (31-32-33-34), Lukens et al, that the

carbohydrate metabolism in the human breaks down; accordingly, whatever it may be, infection (45), *proteolytic* enzymes (48-49), overacting pituitary (31-32-33-38-39-54-55-56-57, hypermetabolism, superalimentation (42-43-44), or *persistent* hyperglycaemia (31-43-50-32-33). anything which finally impairs the ability of the pancreas to make insulin or which extravagantly pushes the insulin mechanism beyond its productive capacity into a state of chronic "fatigue" is compromising normal physiology. That it is possible in normal intact cats by persistent hyperglycaemia to drive the pancreas into "bankruptcy" has recently been shown by Dohan and Lukens(31) who produced a steady hyperglycaemia for thirty-nine days by the intraperitoneal injection of 24% glucose. This was then stopped and the cat remained severely diabetic. Twenty-two days after the cessation of intraperitoneal injections the animal was still severely diabetic with a CO_2 combining power of 11 volumes per cent. The cat was then sacrificed. The pancreas showed the identical degeneration characteristic of severe irreversible

secretion of the anterior pituitary whether thru increased metabolic turnover or thru its growth (54) or *adrenotrophic* (60) factors is diabetogenic. Its excessive activity provokes insulin (-58) extravagance. It causes a decrease in insulin sensitivity (increased insulin resistance) and inhibits the function of hexokinase (7). The end-result of these effects is that of placing an increased demand on the insulinogenic mechanism as well as causing a less efficient use of such insulin as the pancreas is still able to elaborate.

According to Cori (-7) et al insulin inhibits the anterior pituitary gland which in turn is an inhibitor of hexokinase (1-5-7), the enzyme which they find is essential for the phosphorylation of glucose. Apparently without such phosphorylation glucose is inert (-4) and not utilizable by the individual tissue cells. It would seem that the cells can to some extent utilize glucose without the presence of insulin, even if less efficiently than with it; evidently the tissue cells cannot, however, without hexokinase bring the ingested glucose down to the final tricarboxylic acid stage which is the final step before conversion to CO_2 , water and energy for the cells. Assuming that the pituitary gland tends to inhibit the action of hexokinase, if there were no pituitary gland, there should theoretically be no need for insulin in the body. It is obvious even to the clinician that such a theoretical limitation of insulin function is far too simple to explain all of the clinical features in the average diabetic patient. It fails to account for the increased sensitivity to insulin in animals merely deprived of the pituitary gland or in Simmond's disease.

The hexokinase inhibition theory would stress the concept of non-utilization of glucose in the clinical diabetic. Soskin on the other hand emphasizes as predominant in the picture of diabetes the other extreme, the theory of overproduction of glucose by the liver from food moieties other than carbohydrate with little or no inability on the part of the tissue cells to utilize glucose presented to them. A far healthier viewpoint would seem to be that entertained by Best (-38), Haist (-39), and others, that there usually coexist in the diabetic both impaired ** (sub foot-note) utilization of glucose by the cells and an overproduction of glucose from protein and fat. Complete elucidation of what actually takes place in the diabetic is of more than mere academic importance; it affects the entire rationale of what constitutes adequate treatment in the diabetic. From a clinical view-point it is far better, with what knowledge is available, to consider the abnormality in the diabetic as a dual disturbance giving due recognition, however, to the Soskin postulation that one of the main functions of insulin is the regulation of the liver's release of glucose into the blood stream for the tissues.

**If hexokinase functions in adjusting the gradient between external glucose (outside of the cell) and available utilizable (Phosphorylated) glucose within the cell, then it is hard to conceive that a lack of such hexokinase activity could mean other than non-utilization of glucose. That phosphorylation is impaired in the diabetic is well established and easily demonstrable by the constancy of the serum phosphorus content in diabetics during the phase of post-prandial hyperglycaemia when normally there should be a fall in inorganic phosphorus.

pituitary-produced diabetes. Unremitting hyperglycaemia is thus alone without other factors diabetogenic in the cat. There is much clinical evidence in the human that unremitting hyperglycaemia can at least increase the progression of the disease as this is measured by increasing insulin needs on the part of the patient and by the ultimate development of irreversibility under such circumstances in diabetics whose

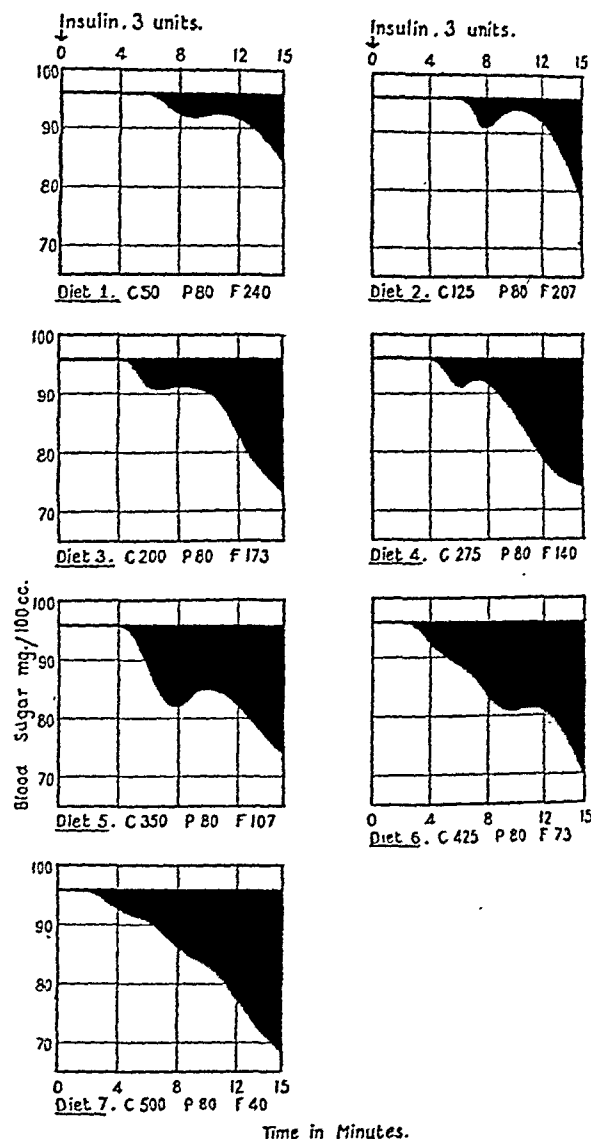


FIGURE I

(From Himsworth, H. P. Clinical Science 2:67, 1935.)

The shaded areas indicate the individual's blood-sugar fall in response to intravenous crystalline insulin after having been on the diet noted under each figure. (All diets equicaloric). Note the marked increase in shading after the diet Ch. 200 as compared with that after diet Ch. 125 and the relatively insignificant increases after diets over Ch. 200 until much higher figures are reached.

disease in its early stages had once been reversible.

Dohan and Lukens(32-33) had previously shown, that in animals in which they had prevented hyperglycaemia from developing by the use of restricted diet, insulin, or phlorizin, it was impossible to produce di-

abetes or typical lesions of diabetes in the pancreas by means of pituitary substance. They had pointed out that pituitary-produced diabetes in its early stages is reversible by these same measures. In the human early diabetes is in part and occasionally totally reversible by these same modalities.

Insulin is consumable. Accordingly, in the early stages of diabetes, an effort should be made to reduce the body's demand for insulin. It is questionable

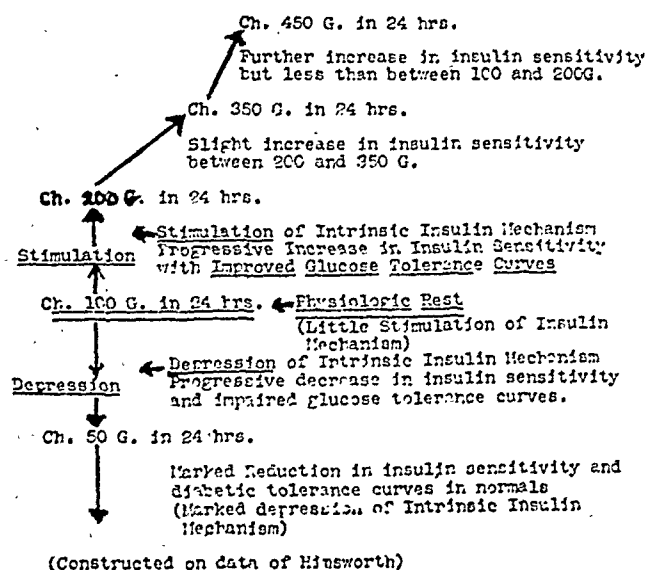


FIGURE II

Himsworth (Ref. 40) has shown that in *normals* increased or decreased sensitivity to insulin in response to dietary carbohydrate corresponds exactly with measured quantitative improvement in the individual's glucose tolerance, suggesting that sensitivity to insulin rather than quantity of insulin available is in the *normal* the more determinant factor in carbohydrate tolerance.

whether in humans direct attack on a hyperfunctioning pituitary will ever be practicable or successful in reducing its harmful activity. There is, however, another very effective method of reducing inordinate demands on the part of the organism for insulin, namely, that of *mild* and painless diet restriction. In general, the more carbohydrate ingested *beyond that amount which favors optimal insulin efficiency unit for unit*, the greater will be the need or demand for insulin.*** It is also well proven that mere excessive ingestion of calorogenic food other than the carbohydrate type will alone increase insulin demands, especially when this excessive ingestion is translated into stored body fat. Thus an irrefutable means of reducing insulin demand presents itself viz. a curtailment of the *calorogenic* food mass ingested. It is too frequently forgotten that the truths established in this respect by Dr. F. M. Allen in the pre-insulin era still hold valid even if their extreme application has softened down to one of easy

***Houssay finds that a diet *rich* in fat (which means high in calories) or an "abundant mixed diet favors the onset and increases the severity of diabetes due to alloxan or to subtotal pancreatectomy." On the other hand, according to Best, Haist (39), and others, starvation (which is actually a diet only *relatively* high in fat, which fat is derived from the fat deposits) made it very difficult to produce diabetes in dogs by means of pituitary substance. The coincidental administration of insulin made it impossible to produce such diabetes in the dog.

moderation. With insulin available, the extremes of undernutrition as originally practiced by this great trail-blazer(61) have become unwarranted and entirely unnecessary. However, the fundamental principle which he established is still valid, and one must recognize that constructive treatment in the *early* diabetic depends in no small measure on initially reducing the total food intake to a point just *at* or slightly but *painlessly* below his actual caloric needs. This holds true whatever may be the relative distribution of carbohydrate(28), protein, and fat of the diet. An overloaded dietary with insulin to cover the excess will *not* effect improvement in the native carbohydrate tolerance of the diabetic. The well-managed diabetic patient from the standpoint of insulin efficiency may neither waste the fuel-foods nor store them in excess. To him must be applied the warning "to live within the day" and not to project *future* fuel needs by excessive storage in the guise of obesity. He may well heed the psalmist's admonition: "Ask not what *shall* we eat or wherewithal *shall* we be clothed." For ideal insulin efficiency and insulin-sparing, the diabetic individual must ingest only that amount of fuel-food which is required for his immediate**** current daily needs.

The second great principle to be applied in the treatment of the average uncomplicated diabetic is that established by Himsworth(40) in 1935 in relation to insulin sensitivity, the principle of stimulation or depression of the insulinogenic mechanism. In *normal* individuals, diets containing less than 100 Grams of carbohydrate in 24 hours tend to be "non-stimulating" of insulin sensitivity; those under 50 G., to be actually depressant to the mechanism; those between 150 G. and 200 G. are markedly "stimulating"; those between 200 G. and 350 G. in 24 hours are somewhat less "stimulating"; between 350 G. and 450 G. there is another sharp wave of "stimulation" but definitely less than between 150 G. and 200 G. (Fig. II)

In the Brooklyn Hospital Diabetes Clinic, Anderson et al. have repeatedly demonstrated that this "stimulating" effect to normal insulin (Fig. I) sensitivity, which increases insulin efficiency unit for unit, occurs in the *diabetic only* when the total calorogenic intake is sufficiently low to permit of adequate chemical control without insulin extravagance***** usually at a

****This concept is graphically demonstrated on frequent occasions in the teaching clinic of the Brooklyn Hospital: Consider the theoretical minimal needs of a given individual at rest to be 1750 Calories. On a diet Ch 200 - P 80 - F 70 - Cal. 1750, let one suppose he spills 4% sugar in his urine. If one maintain the same calorogenic value but change the diet to: Ch 100 - P - 80 - F 115, the patient will still spill 4% sugar. Now if one revert to carbohydrate 200 G. and reduce the calories by fat reduction to 45 G., the urine will frequently become negative without insulin. Reduction of the burden on the insulinogenic mechanism has thus been effected not by a reduction in the carbohydrate of the diet but by virtue of a reduction in its calorogenic value. Subsequently calories can often be increased to actual needs without a return of glycosuria. Excess over needs will reproduce the glycosuria and the further need for insulin.

*****Some will attribute such apparent improvement in insulin sensitivity to fatty infiltration of the liver secondary to the restricted food intake. This is refuted by persistence of the improved insulin efficiency even after the diet has been raised to the optimal needs of the patient.

point just at or slightly below the individual's actual caloric needs. In other words, as a corollary, in the calorically overloaded diabetic individual, the normal "stimulating" effect of a relatively high carbohydrate ingestion is supplanted by an overwhelming depressant effect as this is translated into reduced carbohydrate tolerance, reduced insulin sensitivity (increased insulin resistance) and consequent progressive extrinsic insulin needs.

Accordingly, the clinician has within his grasp the ability to establish relative "rest" of an overtaxed insulin mechanism by reducing the total calories ingested and by holding carbohydrate within the relatively "non-stimulating" range. As soon, however, as chemical control has been accomplished, the "non-stimulating" routine may safely give way to a "stimulating" regimen, raising the carbohydrate of the diet at the expense of the fat but maintaining the same caloric (equicaloric) value of the diet. With chemical control of urine and blood having been established, and with a diet in the range of 200 G. of carbohydrate, insulin-sensitivity now definitely increases. *Pari-passu* with this improved sensitivity to insulin, there develops increased efficiency in the patient's carbohydrate utilization in relation to insulin, grams of carbohydrate utilized per unit of insulin. The initial extrinsic insulin requirements as these may have existed are accordingly reduced.

There can be no excuse whatsoever in the early uncomplicated diabetic for flouting these concepts by way of permitting free diet or the damaging influence of persistent excesses of carbohydrate ingestion. The death-knell to such an illegitimate philosophy in the early diabetic (especially the juvenile type) is finally sounded by the recent work of Lukens—a steady unremitting hyperglycaemia is in itself destructive (31) of islet tissue.

One should never attempt to generalize from the particular, but the above principles are vividly depicted in the following case: In February (Fig. III) 1941, a boy aged 7½ years, came under observation. Both of his parents were diabetic and accordingly they had been advised that all of their children would very probably at some time in their lives manifest evidence of diabetes. The parents routinely had been testing the child's urine and had on several occasions found heavy glycosuria without symptoms except fatigue. With the child having been on a full diet, an Exton-Rose glucose tolerance test showed: Fasting sugar 89 mgms; 30 minutes after 40 G. of glucose, 160 mgms; 30 minutes after a second 40 G. of glucose, 211 mgms with a glycosuria of 1.4%, a mild but prolonged curve without Staub-Traugott effect. The test was repeated for confirmation. The child weighed 58 lbs. (26K.). Theoretical minimal caloric needs at 60 Calories per Kilo were 1560 calories. Diet given: Ch 160 - P 76 - F 70 - Cal. 1569. Protamine Zinc Insulin U3 was given daily. Insulin in minute dosage was kept up until January 1944 when it was discontinued. The diet had gradually been stepped up to: Ch 250 - P 85 - F 66. Growth, weight-gain, and sense of well-being had been satisfactory. Two years after stopping insulin the Exton-Rose test (using 50 G. glucose, repeated in 30

minutes) showed a perfectly normal curve with normal insulin-sensitivity and absence of glycosuria. It is now five years since this child first came under observation. He is rugged, healthy, and of course, not on insulin. He is completely aglycosuric on a diet only qualitatively restricted. *Comment:* What would have been this child's lot, had he been encouraged to follow his own inclinations regarding sugar, candy, and pastry? Obviously, just one more juvenile diabetic!

Feb. 1941 — F.M. - Male; 7½ yrs. of age; wt. 58½ lbs.; ht. 50"; 26 K.
Exton-Rose Test — 40 G. of glucose; repeated in ½ hour.

Time	Blood Sugar	Urine Sugar
Fasting	89 mgm.	0
½ hr. after glucose	160 mgm.	0
½ hr. after 2nd glucose	211 mgm.	1.4%

(Theoretical Minimal Needs: 60 Cal. per Kilo. or 1560 Cal.
Diet given: Ch 160 - P 76 - F 70 - Cal. 1569; P.Z.I. U3).

Exton-Rose Test — 5 weeks later (40 G. glucose repeated in ½ hr.

Time	Blood Sugar	Urine Sugar
Fasting	85 mgm.	0
½ hr. after glucose	169 mgm.	0
½ hr. after 2nd glucose	190 mgm.	0.8%

May 1945 — wt. 80 lbs.; ht. 57¼"; diet Ch. 250; P85 - F66 - Cal. 1934.
Exton-Rose Test — (10-10-45) (50 G. glucose repeated in ½ hr).

Time	Blood Sugar	Urine Sugar
Fasting	90 mgm.	0
½ hr. after 1st glucose	118 mgm.	0
½ hr. after 2nd glucose	164 mgm.	0

FIGURE III

Pre-clinical Juvenile Diabetic (both parents diabetic)

The favorable effect of mild caloric restriction on carbohydrate tolerance is so beautifully demonstrated in the Newburgh (52-53) type of obese adult diabetic (61) that some authorities including Newburgh himself have ventured to state that this syndrome is not diabetes at all. On the other hand, if one permits such a mild glycosuric to follow free unlimited diet, one not infrequently can observe the patient develop into a severe diabetic. The mildness of the original syndrome should never mislead the clinician into careless approach.

The early diabetic, especially of the adult type, usually responds to the regimen of mild dietary restriction because the disease has been treated sufficiently early, at a time when the insulinogenic mechanism can still respond to a reduction of the burden by complete reversal or at least partial functional recovery of the islets. Beta-cell degeneration has not yet progressed to that irreversible state of diabetes ultimately encountered in the average diabetic who has been grossly and persistently ill-managed in the early stages of his disease.

How shall one approach actual treatment of the diabetic patient? It is obvious that with all the variables every patient must be individualized. Handelsman (63) has presented a very satisfactory generalization of the problem of classification which will serve as a prediction of what results may be anticipated. In the final analysis, however, each case is a law unto itself and should be exposed to the method of therapeutic "trial and error." The diet should insofar as is possible be

sufficiently flexible to fit into the tastes of the patient so long as his food habits have not been too flagrantly in error. In most instances, however, it will be expedient for the patient to change established habits and "eat to live" rather than "live to eat." The good diabetic diet is physiologically sound.

The early juvenile diabetic—usually the typical pituitary type of the disease—should, regardless of age, be treated in the vigorous classical manner covering the principles above outlined, the medical attendant demanding as complete blood and urine sugar-control as can be accomplished. The perfection (68-69) of Boyd and Jackson (64) can rarely be attained in clinical practice, but these ideals should be aimed at, for the juvenile is reversible, if at all, only in the early stages of his disease. "Time is of the essence" in these (32) patients, and a relatively short period of free-diet and unremitting hyperglycaemia can establish a state of irreversibility (the Lukens' cat subjected not only to pituitary influence but to an unremitting glycaemia as well—the cat will not develop the disease without liberal diet). The "liberalists" completely "miss the boat" in this type of case.

The obese adult type of diabetic patient on the other hand obviously presents a milder type of disease. The margin of safety is greater in these patients. A blundering management over a considerable period of time will frequently not preclude a considerable degree of late reversibility. That this is true is frequently demonstrated by the victim of free diet who has had his disease sufficiently long to acquire one or more of the complications but who on rational therapy will nevertheless promptly come under complete chemical control (alas, often "after the horse has run away").

The adult type of diabetic should be treated only sufficiently vigorously to get his disease under reasonably complete chemical control, usually an easy chore. He may require insulin in the early stages of treatment but he will frequently (in 50%) if properly treated be able to reduce his extrinsic insulin needs to zero unless complications supervene. While the margin of safety in this type of diabetic is usually wider than in the early juvenile type, free diet can ultimately establish irreversibility of the diabetes with progressive insulin needs even in this type of the disease.

The diagnosis of irreversibility in a given case can be made only by "trial and error" of therapy vigorously applied. This state of irreversibility once established represents "end-organ" failure, structural or functional, or both. It is analogous, as Mosenthal (65) has so aptly pointed out, to the finished product in Alloxan diabetes. It would seem unwarranted in the fully established state of irreversibility to insist on the meticulous chemical control demanded of patients still in the reparable stages of the disease. Ricketts, (34) however, has sounded a note of warning in reminding that the innocuousness of hyperglycaemia from the standpoint of complications has not yet been proven, and the conscientious doctor must, therefore, still "play ball" and not surrender to the extremes of hyperglycaemia.

In the over-all picture there are encountered in the

essayist's experience in the Brooklyn Hospital Clinic approximately four percent of presumably *early* diabetics in whom despite the most meticulous dietary care and insulin management, one cannot establish adequate chemical control. These four percent of patients, for the most part insulin-supersensitive juvenile types of diabetes, are the so-called "brittle cases" in whom adequate insulin administration results in extreme fluctuations between dangerous hypoglycaemia and marked hyperglycaemia—a state of instability incompatible with normal existence either for the patient or for his medical attendant. One reluctantly but advisedly surrenders these patients to a more liberal type of management, sacrificing thereby almost all hope for any degree of functional recovery as this is measured by reduced insulin needs. However, in the other ninety-six percent of cases it is unconscionable not to give the patient an opportunity to approach a more normal physiology, even to do without exogenous insulin if at all possible. Since "trial and error" has proven to be the only certain method of determining which patients will fall into the four-percent category, it is incumbent on the medical attendant to initiate conservative treatment in all cases and vary this in accordance with experience. With few exceptions all patients in the Brooklyn Hospital Clinic are placed on a carefully planned dietary prescription involving *initial* mild caloric restriction (25 Cal. per K. at their tabulated normal weight) and insulin adequate to attain a satisfactory state of chemical control. *Initial* carbohydrate ingestion hovers between 100 and 150 Grams daily (a relatively non-stimulating or "resting" allowance). Liberal protein maintenance is established between 75 and 125 Grams daily. Fat is given only in sufficient quantity to maintain a nutritional intake which is just at or very slightly (45 to 90 G.) below the theoretical minimal requirements for that individual at rest. As soon as the "before meal" glycosuria has disappeared, carbohydrate is stepped-up at the expense of fat, maintaining the caloric value of the diet at a constant level. The scales and sense of well-being of the patient are the best criteria for adequacy of calories which are progressively increased to meet the patient's needs. At no time is the diabetic permitted to vary more than one pound in a week, whatever may be his sense of well-being, since a loss in excess of this represents excessive daily mobilization of body fat. On the other hand, a rapid gain after rebalance of body fluids represents excessive superalimentation in the diabetic. Complete control of the "before meal" glycosuria is the signal for raising the carbohydrate intake to a more "stimulating" level, 150 to 250. Grams. This is done at the expense of the fat, maintaining calories at the same level. One is thereby forcing the patient into a desirable obligatory carbohydrate metabolism at a time when he has demonstrated an ability to negotiate this carbohydrate. Insulin efficiency improves as is indicated by the progressive increase in dietary carbohydrate without commensurate increased insulin administration.

Emphasis is placed on the ante-cibal urines being maintained sugar-free. It is understood that with the

higher carbohydrate values of the diet there may be a transient post-prandial spill-over, analogous to that of an exaggerated alimentary glycosuria. Such spill is not prejudicial to improved carbohydrate tolerance provided there are phases of complete recovery before the next meal and especially complete recovery to normal glycemia thru the night, the post-absorptive period. Nocturnal glycosuria is not countenanced under any circumstances in the reversible diabetic patient (excessive gluconeogenesis). With adequate complete recovery phases, the transient brief periods of hyperglycaemia are compatible with improvement in carbohydrate tolerance and improved insulin efficiency—both of which are readily measureable. In fact, such controlled blood-sugar fluctuations are in themselves probably more conducive to improved function than is the deliberately attained flat 24-hour curve (66). Recovery phases must, however, be insisted on, lest the clinical diabetic become analogous to the Lukens cat with progressive islet degeneration under persistent hyperglycaemia. (31-33).

CONCLUSION

While hyperglycaemia per se has never been proven directly to cause a single one of the more grave complications of the disease, glycaemia is the only real yardstick to measure the adequacy of control of the disease. It is much in the same category as blood urea in the uremic state. Urea is presumably harmless. Unfortunately, the same cannot be said of hyperglycaemia. Persistent hyperglycaemia is destructive of the "end-organ" in carbohydrate metabolism. When one fails to recognize this principle, he is surrendering to the very pathology which it has been his challenge to correct. He may wishfully, if misgivingly, herald as satisfactory the nutritional state and sense of well-being of his patient; he has however, sacrificed every vestige of potential improvement in the patient's own intrinsic insulin mechanism; he has often converted his patient into an irreversible diabetic with heavy and increasing insulin needs. Let it not be said that the medical attendant thru paths of lessened resistance has deliberately created this state of irretrievable failure.

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DISCUSSION OF DOCTOR GEORGE ANDERSON'S PAPER BY MILTON B. HANDELSMAN.
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BROOKLYN, N. Y.

THIS presentation by Dr. Anderson should fulfill a need long felt by those who are teaching the problems involved in the management of diabetics. We have been given no simple formula to cover every case of diabetes. The author, instead, has presented us with broad principles that place in proper perspective the problems encountered in practice every day; he has shown how these principles can be applied practically with due regard to each individual patient's need.

In the opening of the paper, we heard a clear expression of what should be our aims in treatment. With due regard for exceptions that are known to be benefitted by a mild hyperglycaemia, it is demanded that we maintain our diabetic patients without glycosuria and hyperglycaemia yet not at the expense of poor nutrition. Although these rigid criteria have been considered unnecessary by some, our experience leads us to concur in Dr. Anderson's demands. A progression in the diabetic state occurs if there is an excessive continuing demand for insulin and this progression is one that has practical clinical significance. We first met this problem in 1934 when the clinic in the Long Island College Hospital was reorganized. At that time, we were in the process of changing the dietary regimen of all patients from high-fat low carbohydrate diets to low-fat, higher-carbohydrate diets. For the most part we found an amazing "recovery" of glucose tolerance that was generally reported by all workers when such dietary changes were brought about. However, there were "failures" in whom tolerance for carbohydrate was not improved and in whom the change to a diet with higher carbohydrate content necessitated considerably increased dosage of insulin despite the reduction of the dietary fat content. A study of these failures showed predominately three groups: (1) obese patients, originally mild, who had had their diabetes for over ten years and had remained obese all of the time; most of these were the known "cheaters." (2) The young adults between the ages of 20 and 60 years who were thin at the onset of the diabetes and who had had the disease for over 10 years and (3) several of the "labile" adolescent patients. Again, later, when protamine zinc insulin was introduced, we met with more "failures." It was generally recognized that it was much simpler to commence treatment with this insulin in a new patient than it was to change a patient who had been receiving regular insulin for many years over to a regimen with the long-acting insulin. In the latter, the most bizarre mixtures of insulin reactions and hyperglycaemia with glycosuria occurred, necessitating in some a return to the multiple doses of unmodified insulin. In our studies, the "failures" again fell into the same class of patients mentioned above as showing an apparent *fixed* pattern of decreased carbohydrate tolerance when diets were changed. The "failures" encountered when new and better modalities of treatment were introduced,

in our experience, occurred in patients in whom there had been a progression in the diabetic condition, and who finally arrived at a stage where there seemed to be a loss of the patients' own homeostatic mechanism of carbohydrate regulation. The total loss of this mechanism is probably the cause of the lack of response to external changes in the diabetics who have neglected treatment or who have been improperly treated for a *long time*. This can occur in patients who need only 25 units of insulin a day as well as those who require as much as 100 units.

It must be pointed out that this homeostatic control is *not* lost in most well treated diabetics; in fact it can even be found in severe cases receiving large doses of insulin. Clinically it can be recognized when a diabetic who has been well controlled goes to an occasional banquet where he will eat excessively and yet find no recurrence of glycosuria or hyperglycaemia the next day despite the fact that no extra insulin is given. Or it is seen when a well controlled diabetic contracts a severe cold with fever and yet does *not* spill glucose or acetone in the urine on the same diabetic regimen. Recently, we attempted to show that the glucose-regulatory effect of insulin administered to a diabetic is more or less determined by an ability retained by the patient himself to maintain good glucose homeostasis. The administered insulin gives a glucose-regulating response dependent on the type of diabetes which the patient has. Thus, there are diabetics who are easily "controlled" and there are others in whom it is almost impossible to obtain a satisfactory physiological level of control since ambitious insulin therapy usually produces wide swings from hyperglycaemia to hypoglycaemia.

Dr. Anderson has pointed out the experimental and clinical evidence that allows planning to prevent the conversion of a simple diabetic into a difficult case, namely that in the patients with early diabetes we must decrease any existing demand on the pancreas to secrete excessive amounts of insulin and thus prevent a total collapse of the patient's insulinogenic mechanism. The insistence that treated patients keep the urines sugar-free and the blood sugar at a normal level serves two purposes: (1) it insures "rest" for the pancreas inasmuch as hyperglycaemia is known to stimulate the pancreas to secrete insulin and (2) it is an indicator that other factors which have been excessively demanding insulin, are under control.

The latter point is well illustrated, as Dr. Anderson pointed out, in the adult obese group of mild diabetics which form about 60% of the diabetic population in our clinic. When these patients are treated soon after the disease manifests itself, reduction in weight by means of low caloric diets invariably leads not only to a disappearance of glycosuria and hyperglycaemia but also to a remarkable return of ability to consume carbohydrate. Although this has been known to clinicians since the studies of Rollo in the 18th century, only recently has it had satisfactory explanation. Stettin has shown that insulin is required to form large fat stores from carbohydrate foods; thus obesity is probably maintained in a patient at the expense of a heavy demand for

insulin. A restriction of food, halting this process of fat-formation, should decrease the demand for extra insulin and allow the overstrained pancreas to maintain its reserve strength.

The ease with which obese adults can be treated and controlled when seen early stands out in contrast to the difficulties met in those who have neglected management for many years and then later apply for treatment. In the adult, this time interval is long, probably ten years or over. Dr. Anderson's plan of treatment for these patients is sufficiently liberal after the original period of malnutrition to allow them to live both comfortably and happily during that time while preventing a "progression of the diabetes" with its difficulties as mentioned above.

In the adolescent diabetic and in young active adults with diabetes, other physiological factors come into play. Again, recent physiological studies show that the insulin demand is great in these states. For instance, the experimental work of Young suggests that the growth process stimulated by the anterior pituitary demands insulin for adequate development. We should thus suspect that physiological growth seen in youngsters might impose a strain on a pancreas with low reserve capacity; this fact has been clinically substantiated by Priscilla White, who pointed out that diabetes in childhood most often manifests itself after a period of accelerated growth. Evans and his coworkers have collected evidence that insulin is required for the protein anabolism induced by the anterior pituitary hormone, adding another probable factor of increased demand for insulin in childhood and in young adults. We have as yet no idea as to how much insulin is required for these physiological processes, but we can see the wisdom in Dr. Anderson's advice that for these

diabetics, diets observing the classical laws of nutrition be given with adequate insulin coverage. Many young diabetics when discovered early and treated promptly are not severe as is generally thought. The large number of unsuspected mild young diabetics newly discovered by the Selective Service Board suggests that we have been diagnosing our juvenile diabetics too late. Neglect in treatment in the juvenile diabetic leads to a far more rapid progression and increased severity of the disease than is seen in adults. Early treatment of the mild patient *with insulin* can prevent this progression in many patients. The maintenance of sugar-free urines and a normal blood glucose is the only way one can be sure that one is "sparing the patient's pancreas" or by giving a sufficient dose exogenous insulin for normal growth and protein anabolism as well as for the maintenance of the hepatic blood sugar regulating mechanism at a normal level. Unfortunately intercurrent infections, fractures, acidosis etc., can undo the good work accomplished by good regulation and lead to a rapid progression of the disease, but this should not lead to a fatalistic attitude that it therefore does not pay to treat the early cases vigorously. Certainly, Tolstoi's demonstration that severe diabetics can be kept with P.Z.I. in adequate nitrogen balance despite glycosuria has given us more courage in treating in a more lax fashion the patients who have already progressed to the severe labile stage. We must recognize that for most of these patients we can accomplish little more even when we observe rigid standards.

In closing, I must state that Dr. Anderson's remarks concerning the prevention of arteriosclerosis in diabetes by treatment summarizes the situation; we must withhold opinion until we know the cause or causes of arteriosclerosis.

Book Reviews

Concise Chemical and Technical Dictionary. Edited by H. Bennett. \$10.00, Pp. 1055, The Chemical Publishing Co., Inc., Brooklyn, N. Y.

This valuable reference book contains 50,000 definitions and deals with terms used in chemistry, metallurgy, pharmacy, plastics, physics, mineralogy, electricity, engineering, etc. Naturally it contains many medical words and biological nomenclature. Apart from those actually engaged in the lines mentioned, this dictionary is very valuable to anyone whose reading spreads over into these fields. Today, even the large general encyclopediae fail us, and we need a set of special dictionaries to keep up with the specializations of our age.

Narcotics and Drug Addiction. By Erich Hesse. (\$3.75). Pp. 219. New York, Philosophical Library, 1946.

The author writes that he has endeavored to convey a pharmacological-toxicological knowledge and a general outline of the medical significance of narcotics and stimulants. In a readable style he outlines the various properties of the major narcotics and of stimulants such as coffee, tobacco, alcohol, mate and cola. Emphasis is placed on the problems of addiction. Prohibition without dissemination of knowledge about the dangers of indulgence is bound to be a failure. While the book will be found quite useful, especially as a source of some European literature, there are several question-

able statements which are passed off as facts. For instance, a pharmacologist who spent some time in Oceania told this reviewer that in his opinion the chapter on intoxicating pepper or Kava-Kava contains an account of the action of the drug which is entirely at variance with its known properties. The deleterious effects of over-indulgence in some of the alkaloids are properly emphasized but unfortunately the author takes a crusader's attitude towards the eradication of all stimulants used in everyday life, such as alcohol and tobacco.

Dietotherapy. Clinical Application of Modern Nutrition. Edited by Michael G. Wohl. Pp 1029, Philadelphia, W. B. Saunders Co., 1945.

This volume, consisting of 44 well-written chapters, is the cumulative effort of some of our foremost nutrition scientists and clinicians to write an authoritative and up-to-date discussion of every aspect of nutrition. While success is not entirely theirs, the authors have certainly produced a book to be read profitably by research workers and physicians alike who have anything at all to do with nutritional problems. The material is well-chosen and divided into three main sections: normal nutrition, nutrition in periods of physiologic stress (such as during pregnancy, in infancy and old age, in athletes, etc.), and nutrition in disease. Thruout, the various contributors, of whom there are 58, have kept their discussions anchored to a physiologic basis so that cook-book rule-of-the-thumb accounts are presented in almost the absolute minimum amount. Each chapter ends with an extensive bibliography, aiding those who wish to pursue particular questions down to the earlier work. The index is excellent and certainly most helpful. (So many books have been published recently with a poorly prepared index!) A number of useful and practical appendices pertaining to caloric values, vitamin and mineral content, etc. of different foods and edibles are included. Doctor Wohl and his contributors are to be complimented on producing a volume which should fill a gap on many a doctor's bookshelf.

Practical Physiological Chemistry. By P. B. Hawk, Ph. D., B. L. Oser, Ph. D. and W. H. Summerson, Ph. D. Pp. 1323, Twelfth Edition, \$10.00. The Blakiston Company, Philadelphia and Toronto, 1947.

"Hawk's Practical Physiological Chemistry" is an old standby familiar to most medical men who were

formerly medical students. It has grown in volume during the past thirty years, has added two new authors, but remains the eminently useful book which combines theory with laboratory practice. New subjects covered in this Twelfth Edition include the polarograph, isotopes, "sulfa" drugs, metabolic antagonists and antibiotics, the Warburg tissue-slice technique, photometric analysis, and the newer vitamins. The book is ideal for the medical student. Incidentally, the format is attractive and the binding very sturdy and can be cleaned with soap and water.

Le Diabete Et Sa Pathogenie. By L. Ambard., Masson et Cie, Paris, 1947, 240 fr.

This is a good review of diabetes which devotes proportionate space to etiology, pathology and treatment. The enzyme theory of diabetes receives considerable attention. Treatment with old insulin and those of slow absorption parallel present practices in the U.S.A.

Experiences With Folic Acid. By Tom D. Spies, M.D. pp. 110, (\$3.75), The Year Book Publishers, Inc., Chicago, Illinois.

Dr. Spies has provided a detailed and very interesting account of his own important and fruitful researches on the anti-anemia effects of folic acid which he refers to as "the newest member of the vitamin family". Folic acid acts as a specific in curing the macrocytic anemias (pernicious anemia, sprue, nutritional anemia, pregnancy anemia, etc.) although apparently it has no effect on the neurological changes in Addisonian anemia. Spies' work was and is characterized by great detail work in the diagnosis and very extensive clinical trials of therapeutic material. He regards folic acid as probably a part of an enzyme system, but in the case of persons with Addisonian anemia, their bodies seem incapable of utilizing folic acid if it is fed to them as a constituent of some other substance. Apart from its practical value as a guide to folic acid therapy, this monograph is an excellent review of the macrocytic anemias, and is highly recommended.

Book Received

The Pharmacopoeia of the United States of America.

Thirteenth Revision. Pp. 957, Mack Publishing Company, Easton, Pa., 1947.

Abstracts of Current Literature

(Microfilm copies of papers may be obtained from the Microfilm Service of the Army Medical Library at 25c per each complete article, not exceeding 25 pages in length—and 10c for each additional 10 pages or fraction thereof. Prepayment is not requested. Remittances may be made with subsequent orders and in such manner as found most convenient. Address—Microfilm Service, Army Medical Library, Washington, D. C.)

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CLINICAL MEDICINE

BOWEL

HALLENBORG, L. C. AND LOVELACE, W. R.: (Aber-
rant gastric mucosa and pancreatic tissue in bleeding.
(Meckel's diverticulum.) *Proceed. Staff Meet. Mayo
Clinic*, v. 22, p. 53, Feb. 5, 1947.

Meckel's diverticulum, though not occurring fre-
quently, can give rise to complex and unusual clinical
symptoms, usually when aberrant or heterotopic tissue
is present in the diverticulum. About one quarter of
the people with diverticula show symptoms and the di-
verticulum occurs in about 2 to 3 per cent of the
general population.

The commonest clinical picture is periodic bouts of
severe intestinal bleeding with or without pain. In-
volvement of intestinal loops around the diverticulum
gives rise to acute obstruction. Symptoms of acute ap-
pendicitis are common.

Heterotopic tissue was found in 27.6 per cent of 150
cases with Meckel's diverticulum that came to autopsy.
Gastric mucosa is present in about 15 per cent of all
cases but in cases showing clinical symptoms the inci-
dence may be as high as 60 to 70 per cent. Pancreatic
and duodenal tissue each occur in about two per cent
of all diverticula.—W. D. Beamer.

MONAT, H. A. AND BATZLI, J. H., JR.: (*The signifi-
cance of Hanger's test (cephalin-cholesterol floccula-
tion test) in disorders of the stomach and colon*. *U. S.
Naval Med. Bull.*, v. 46, p. 1568, 1946.

Monat and Batzli studied two groups of patients
with gastro-intestinal disturbances by cephalin floccu-
lation test to determine latent liver damage. In the first
group 41% of 27 patients with chronic gastritides and
ulcers had a positive Hanger's test with 2 plus as the
highest individual record. The second group was a
lower bowel group and was subdivided as follows:
7 of 8 ulcerative colitis cases or 87½% were positive
with 3 plus as the highest record; 3 of 5 lower bowel
infestation with either *Giardia lamblia*, *E. Nana*, and
E. coli, were positive for a percentage of 60; there
were 21 cases of non-specific diarrhea, mostly psycho-
somatic of over 2 years duration with 14 or 66⅔%
positive Hanger's; and of 12 patients with amebiasis
without obvious liver abscess 10 or 83⅓% were Hanger-
Test positive. The authors call attention to the higher
liver involvement in large bowel disturbances than in
stomach and small intestine. The suggestion is offered

that the colon is possibly concerned with nitrogen
metabolism and its imbalance by disease is reflected in
damage to the liver.—*J. M. Waldron.

Amount 38 orthopedic controls 5 or 18% were positive.

PAINE, J. R.: *Intestinal obstruction*. *Internic*, v. 13,
p. 120, March, 1947.

This is a brief review of the subject. Hernia and ad-
hesive bands are the most common causes of intestinal
obstruction in this country, while intussusception ap-
pears as the most common in Japan. Wangersteen's
clinical and pathological classification of intestinal ob-
struction is presented. Treatment consists of relief of
distension by decompression, restoration of fluid and
electrolyte balance, administration of blood when shock
is impending and release of the obstructing mechanism.
The release from distension by continuous aspiration
may reduce edema and frequently relieve the obstruc-
tion without the necessity of operation. However, re-
currence of the obstruction is likely.—I. M. Theone.

SIMPSON, O. G.: *Acute appendicitis in the aged*.
Brit. Med. J., v. 2 p. 986, 1946.

This symptomatology of acute appendicitis in pa-
tients past the fifth decade is somewhat different from
that in younger people. Pain is generally present but
is not well localized. The pain is milder than in younger
patients but becomes severe when peritonitis is present.
A slight fever may be present. Other well-recognized
symptoms noted in younger patients with appendicitis
are usually absent. These include nausea, vomiting and
rapid pulse. Tenderness and rigidity as well as the pain
shown on rectal examination are usually absent or only
present to a moderate degree.

In consequence of the absence of many of the well-
defined signs and symptoms associated with appendi-
citis in the younger age groups the elderly patient of-
ten is not recognized as being ill until peritonitis has
set in. At this stage the mistaken diagnosis of intestinal
obstruction is usually made. From 1 to 2 per cent of
the cases of acute peritonitis occur in patients past
sixty years.—F. E. St. George.

DOLKART, R. E., DENTLEY, M. AND BARROW, L. L.
Management of the irritable bowel syndrome. *Illinois
Med. J.*, v. 90, p. 287, 1946.

The paper reports on 29 patients of a large series in
whom complete medical studies were done. All subjects

had constipation and experienced abdominal distress. One patient had diverticulosis, one had a duodenal diverticulum, two showed evidence of healed peptic ulcer, and the remainder were roentgenologically negative.

Saline cathartics, dietary measures, hydrophilic muciloids and hydrophilic gums were compared for effectiveness to bring about more normal bowel habits. Psyllium muciloid was found the most effective. Even this, however, should not be given when lesions reacting unfavorably to bulky stools are present. Other medications, such as saline cathartics and liquid petrolatum, are distinctly undesirable, particularly if taken over a long period of time. No one substance by itself may be considered as a substitute for good principles of bowel management but the hydrophilic muciloids come closest in being of important value as adjuncts. Regular bowel habits and adequate fluid intake must be stressed.—F. X. Chockley.

PANCREAS

MOLANDER, D. W. AND BELL, E. T.: *Relation of cholelithiasis to acute hemorrhagic pancreatitis.* (*Arch. Pathol.*, v. 41, p. 17, 1946.)

Necropsy records of 41,333 people were studied. It was noted that acute pancreatitis in the absence of gallstones had been reported in 66 per cent of the men and 33 per cent of the women, so that gallstone formation is not essential to acute pancreatitis. However, since gallstones occur about 6 times as frequently in cases of acute pancreatitis than in non-pancreatic disease, the authors conclude that some causal relation exists between the two.—H. Stilyung.

KENNEDY, R. L. J.: *Cystic fibrosis of the pancreas.* (*Nebraska Med. J.*, v. 31, p. 493, 1946.)

The etiology of cystic fibrosis of the pancreas is not clear though both an infectious basis and a mechanical basis have been suggested. Respiratory symptoms, such as a hacking or paroxysmal cough, is present in all cases before the third year and in about half of the cases shortly after birth. A croupy cough with rales suggesting laryngeal and pulmonary involvement is heard. The child becomes often dyspneic and cyanotic. The fingers become clubbed. The abdomen becomes distended and the thorax raised because of emphysema. The stools are both frequent and voluminous. The feces are bulky, frothy, oily, and light colored, suggesting large quantities of undigested fat. In spite of a large food intake the child fails to gain weight. The commonest mistaken diagnosis is that of coeliac disease from which the condition can be differentiated only by numerous clinical-laboratory examinations.

The disease is characterized by a loss in ability to digest and absorb proteins and fats and by a marked vitamin A deficiency. The diet therefore should consist of predigested protein (amino-acid mixtures), carbohydrates, and some fats. Large doses of vitamin A should be given intramuscularly. Pancreatin is ad-

ministered at meal times. The broncho-pulmonary infections have been treated with penicillin and inhalation of penicillin vapors. Of 28 children, 18 died. All were under 7 years of age, most of them were under two years of age. Improvement was shown by some with the treatment but recovery has not been attained.—H. Stilyung.

LIVER AND GALLBLADDER

BYWATERS, E. G. L.: *Anatomical changes in the liver after trauma.* (*Clinical Science*, v. 6, p. 19, 1946.)

The author has presented, from the material of 42 cases, an account of the anatomical changes found in the liver following crush injury, severe fracture and several other types of trauma. These findings are correlated with the functional aberrations during life.

A high proportion of cases showed necrosis of the central and mid-zonal cells of the lobule, which histologically appeared to date from the time of the injury. Necrosis occurs usually in the most severely injured, judged by blood pressure readings and the amount of transfusion fluid given and probably results from restricted blood and oxygen supply to the liver. Necrosis was seen more often in the left lobe and is explained by differences of blood supply from the surrounding portal tracts. Mitoses were seen only in those patients who died six days or more after injury, but not in those dying before this time.—Joseph Medoff.

WOOD, D. A.: *Pathology of acute epidemic hepatitis: early stages.* (*Arch. Pathol.*, v. 41, p. 345, 1946.)

Reports on ten fatal cases are given. Of these, 6 patients had received wounds 3 to 4 months earlier so that they may have had "homologous serum jaundice" rather than the probably separate entity "acute epidemic hepatitis." Apparently both diseases are due to the same virus and differences in incubation periods are determined by the route of infection. Eight of the patients died within 2 to 10 days of onset of illness. Acute yellow atrophy was seen in all livers. On the second day of illness the liver cells were swollen and detached but by the 10th day most of the cells were autolyzed and the debris had been removed. Lymphocytic and monocytic inflammatory reactions were shown chiefly during the earlier stages of the illness. The spleen and regional lymph nodes were enlarged with frequent necrosis in the splenic Malpighian bodies and lymph nodes. Patients living less than ten days showed almost no nodulation of the liver.—G. Klenner.

PATEK, A. J.: *Use of vitamin B complex in treatment of cirrhosis.* (*New York State J. Med.*, v. 46, p. 2519, Nov. 1946.)

The etiology of Laennec's cirrhosis is still unsettled but there is much evidence that it arises on a nutritional basis. The disease is not always chronic but may develop within a short time of several months. If medical

treatment is undertaken early there is a good chance for recovery. Jaundice, asciteis, splenomegaly and vascular spiders are evidence of an advanced stage of the disease. Treatment of 124 patients in the decompensated stage was undertaken. Bed rest, restriction of salt intake, drinking of about two liters of fluids daily and a high calorie diet were tried. Protein intake was high while fat and carbohydrates were moderate. Crude vitamin B complex preparations and large doses of brewers yeast were given. Distinct signs of clinical improvement were noted in 51 of the patients.

—G. Klenner.

STERN, K. TYHURST, J. S., AND ASKONAS, A. B.: *Note on hippuric acid synthesis in senility. (Am. J. Med. Sci., v. 212, p. 302, 1946.)*

Quick's intravenous test was used on 3 consecutive days in senile patients. Ten subjects, 4 of whom had anorexia of psychologic origin, acted as controls. In the control series, the output of hippuric acid was within the accepted normal range in the first and third day. On the second day, when glycine was given before the sodium benzoate injection, the hippuric acid output was normal in 5 cases and high in one. The anorexia cases showed either an increase or a decrease when glycine was given: otherwise the test was normal. In the senile patients the initial hippuric acid output was low in 10 cases, and was increased in 9 of these by the addition of glycine. The authors concluded that impaired benzoic acid detoxication by the liver in old age was due to impairment in providing adequate glycine for the process rather than to impairment in the conjugation process.—M. H. F. Friedman.

ULCER

VINCI, V. J., SPEIGHT, H. E., BELLA, L. L., AND BUCKLEY, W. E.: *Management of peptic ulcers with a high protein, high caloric diet. (Connect. Med. J. v. 10, p. 281, Apr. 1946.)*

A diet of high caloric value and high in protein content was employed in 30 cases of peptic ulcer. Nine of these cases were considered for surgery and were treated with this diet preparatory to operation. The caloric value of the diet was 3,760 calories, and consisted of 287 grams carbohydrate, 275 grams protein and 168 grams fat. Supplementary feedings of strained cooked cereals and soft-boiled egg brought the total caloric intake to 4,078. The patients were kept at complete bed rest.

Nineteen of the patients responded well. Symptomatic relief was prompt and ulcer healing was noted by X-ray in 18 to 21 days. In the nine patients given the diet before operation it was found that tissue edema was reduced, surgery was less difficult and the post-operative convalescence greatly accelerated.

—D.A. Wocker.

FISCHER, A., CLAGETT, O. T., AND MACDONALD, J. R.: *Coexistent duodenal ulcer and gastric malignancy. (Surgery, v. 21, p. 168, Feb. 1947.)*

Forty eight patients having proved coexistent lesions were seen at the Mayo Clinic between June 1911 and January 1945 inclusive. The criterion for the presence of a duodenal ulcer was its observation at operation or necropsy, not by roentgenographic demonstration. The carcinoma of the stomach was verified histologically except in four instances. There were twelve other cases in which the presumptive diagnosis of both lesions coincidentally present was made but not proved by surgical exploration for example. During this period, 13,000 patients with carcinoma of the stomach and 45,000 with duodenal ulcer were seen, as well as 600 with coexistent duodenal and gastric ulcers. Thus the rate of coexistent duodenal ulcer and gastric malignancy is 1 in 938 or 0.1 per cent. The average age was 52.9 years, thirty-nine were men and nine were women. Roentgen diagnosis of both lesions was made in twenty-two of forty-six cases. Twelve patients were alive five years after the diagnosis was made. And two of these were alive twenty and twenty-one years.

ULCER

GREENBLATT, I. J., AND COHN, T. D.: *Azotemia in gastro-intestinal bleeding. (Am. J. Med. Sci. v. 211, p. 565, May, 1946.)*

The blood urea nitrogen is often greatly elevated following episodes of hemorrhage from the gastro-intestinal tract. This so-called pre-renal azotemia was studied in 8 men who drank their own blood (citratd) drawn from a vein. An intake of 580 cc. of blood by 5 subjects resulted in no significant changes in either blood urea nitrogen levels or renal urea clearance rates. However, an intake of 800 cc. of blood by 3 subjects resulted in a greatly increased blood urea nitrogen level and in a decrease in urea clearance. Plasma protein levels and the hematocrit values were decreased.

Since the increase in blood urea nitrogen was not due to the ingestion of a protein (blood) alone, it is probable that the renal failure due to shifts in fluid balance resulting from hemorrhage is in part responsible for the azotemia.—G. Klenner.

BERNSTEIN, B. M.: *Histamine in the treatment of peptic ulcer. (Rev. Gastroenterology, v. 14, O. 129, Feb., 1947.)*

Ninety-two unselected patients with gastric, duodenal, and marginal ulcers were treated by daily subcutaneous injections of 0.3 mg. of histamine phosphate. In addition the patients were kept on the usual bland diet with frequent milk feedings. Gastric analysis, when done, showed in most instances the expected rise in gastric acidity. In the group there was one fatality, a woman who developed a perforation and hemorrhage. One male perforated at onset of treatment, two developed easily controlled hemorrhage, and a few had tarry stools which did not interrupt the treatment. Sixty-one of the cases had complete relief from ulcer pain after the fourth injection and a total of 76 were completely relieved after the tenth. Eight failures were recorded. It is believed

that these results indicate the greater importance of the vascular origin of the pain over that of the acid-pepsin mechanism. — W. D. Beamer.

CUMMINS, G. M., GROSSMAR, M. I. AND IVY, A. C.: *Healing time in peptic ulcer.* (Bull. U. S. Army Med. Dept., v. 6, p. 288, 1946.)

The authors could find little in the medical literature relating to the healing time of peptic ulcers. Fluoroscopic and roentgenographic studies at commencement of treatment and during periods following treatment were made in 63 cases of duodenal and 6 cases of gastric ulcers among army personnel. The patients ranged from 22 to 66 years in age, the average being 31 years.

All patients were kept on the same regimen. Bed rest was enforced for the first 3 days and restricted activities during the following days. For the first 28 days the patient was given alkaline powders every 2 hours during the day and at night if in distress. Six ounces of a milk-and-cream mixture were given every 2 hours during the day for the first 28 days, and later only between meals. Special soft diets were given during the first 28 days. At first the meals were numerous but small, later they were given only 3 times per day. During the first 28 days tincture of belladonna, phenobarbital and vitamin concentrates were given.

The average time taken for the duodenal ulcer crater to no longer become visualized was 40 days, ranging from 13 to 230 days. This time of healing could not be correlated with the following: duration of ulcer symptoms, age of patient, incidence of recurrence, or size of the crater as found at commencement of therapy. — John Moffitt.

SURGERY

MAIMON, S. N. AND PALMER, W. L.: *Gastric cancer: laparotomy, resectability and mortality.* (Surg. Gynecol. Obstet., v. 83, p. 480, 1946.)

Resection is the only known effective procedure for treating cancer of the stomach. The lower mortality and the longer postoperative survival in an increasingly greater number of patients attests to the validity of this statement. The paper by Maimon and Palmer is an attempt to evaluate the figures reported by different surgeons, with particular attention paid to a series of patients from the University of Chicago institutions.

From 1927 to 1944 there were 576 patients examined who had gastric cancer; of these 466 accepted the advice of having (or not having) an operation. Laparotomy was performed in 389 or 83.5 per cent of the cases: resectability was found to be 52.1 per cent in these 389 cases (or 203 patients). Of the 203 patients having resection the survival rate was 73.7 per cent.

On the basis of unselected cases, the mortality in patients with partial resection was 22.6 per cent prior to 1940 and 16.3 per cent since 1940. Autopsy findings in patients dying post-operatively showed resection to have been complete in 25 per cent of the dead patients, in so far as residual carcinomatous tissue could not be

found. The main cause of immediate death was peritonitis.

The authors conclude that surgery offers the only cure, that palliative resection is worth while, that mortality rates are decreasing (due to greater surgical skill and experience, as well as chemotherapy, etc.), and that resectability rates are high. However, "the outlook for prolonged survival continues to be rather limited." — I. M. Theone.

HEUER, G. J.: *Surgical aspects of hemorrhage from peptic ulcer.* (New England J. Med., v. 235, p. 777, Nov., 1946.)

Massive hemorrhage from a peptic ulcer was the reason for admission of 337 patients to the hospital. Operation during bleeding was performed on 31 patients with 9 deaths. There were also 18 deaths in patients not subjected to surgery. The fatal duodenal hemorrhage was from the posterior duodenal wall while the fatal gastric hemorrhage was from the lesser curvature of the stomach. The prognosis is bad for the patient if improvement is not prompt when the patient is placed under complete bed rest, morphine, blood transfusions, and restriction on oral intake of food and fluids. Excision of the ulcer and gastric resection gave the best results when done within 48 hours from the time hemorrhage began. Ligation of the blood vessels supplying the ulcer area was not effective in arresting bleeding episodes permanently. Whether surgery should be performed or medical management alone continued in patients whose hemorrhage was controlled by medical regimen is a question to be decided only by study of the individual case. — G. Klenner.

SWEET, R. H.: *Subtotal esophagectomy with high intrathoracic esophagogastric anastomosis.* (Surg. Gynecol. Obstet., v. 83, p. 417, Oct. 1946.)

Radical excision of the esophagus was carried out on three patients with lumen obliteration produced by chemical burns. In one patient the anastomosis between the proximal esophageal stump and stomach was made as high up as the jugular notch. In the other two patients the obliterated region of esophagus was lower so that the anastomosis could be made below the level of the aortic arch. The three patients recovered esophageal functions. The author recommends esophagectomy with high intrathoracic reconstruction of the esophago-gastric junction as superior to external esophagoplasty. — I. M. Theone.

HALLATT, J. G.: *Appendectomy by inversion.* (Permanent Foundation Med. Bull., v. 4, p. 156, 1946.)

Often in the course of an abdominal operation for some other reason the surgeon may select to remove the appendix as a prophylactic measure. Hallett has used an inversion procedure successfully in 100 cases. The appendix is freed from its attachments and the distal end is invaginated into the cecum. The cecal

wall is then closed with a single mattress suture. The appendix cannot be inverted when it is inflamed nor when the lumen is so constricted that invagination is difficult. The procedure has the distinct advantage in that the bowel is not opened so that contamination by bowel contents is avoided. The appendix, deprived of most of its blood supply during the process of freeing it from its mesenteric attachments, soon sloughs away and is expelled in the stool in about two weeks. — F. X. Chockley.

EXPERIMENTAL MEDICINE

PHYSIOLOGY

FURCHGOTT, R. F. AND SHORR, E.: *Sources of energy for intestinal smooth muscle contraction.* (*Proc. Soc. Exp. Biol. Med.*, v. 61, p. 280, March, 1946.)

The effect of certain substances on the restoration of the contraction amplitude of smooth muscle strips allowed to contract in the presence of aerated Krebs-Heinsscheit solution was studied. The relative ability of these substances to restore amplitude was compared to that of glucose.

Of the substances studied, acetic acid and pyruvic acid succeeded in restoring contraction amplitude completely. The activity of other carbohydrate solutions, especially those postulated in the Meyerhof cycle, was either low or absent. This may be explained by their inability to pass cellular membranes. The members of the Krebs tricarboxylic acid cycle exerted little restorative effect, except for oxalacetic acid. This effect may be due to the inability of the cells to decarboxylate these compounds to readily oxidizable pyruvic acid. The authors feel that these results do not support the present theories of metabolic participation of the above cycle in smooth muscle metabolism.

Amino acids exert little effect on the smooth muscle and this seems to indicate a lack of ability to deaminate these acids into their readily utilizable hydroxy homologs. Ketone bodies likewise exert little effect. Diacetic acid is the only one utilized and that to only a slight extent. — J. Moffitt.

MAGEE, D. F.: *Some observations on the pharmacology of the sphincter of Oddi.* (*Quart. J. Pharmacy and Pharmacol.* v. 19, p. 38, March, 1946.)

In an effort to study the pharmacodynamics of the sphincter of Oddi, the terminal portion of the bile duct of the sheep and ox was isolated and split longitudinally and opened out to record the contraction of the circular muscles. When first set up the muscle fibers did not show rhythmical contraction; however, adrenalin in dilute solutions caused rhythmical contractions consistently. This response was abolished by Yohimbe. Acetylcholine added to the perfusate caused a less marked contraction, which was abolished by atropine. The duodenal musculature contracted when perfused with acetylcholine and relaxed with perfusate containing adrenalin. It is therefore concluded by these authors that the duodenum and sphincter musculatures are functionally separate entities. The reaction of the gall-

bladder was the reverse, i. e. adrenalin had no effect on the gall bladder whereas acetylcholine caused marked contractions. Morphine was ineffective on the isolated sphincter mechanism of either the ox or sheep. Atropine and theophylline produced relaxation of the contracted sphincter. — Wm. J. Snape.

GREGORY, R. A.: *Changes in intestinal tone and motility associated with nausea and vomiting.* (*J. Physiol.*, v. 105, p. 58, July, 1946.)

Intestinal tone and motility were recorded from Thiry-Vella loops in dogs by means of inserted rubber balloons recording through water manometers. Subcutaneous doses of apomorphine in the minimal dose required to produce nausea and vomiting were given. Apomorphine in such doses had no effect on either tonus or motility when there was neither nausea nor vomiting. Nausea was accompanied by rapid fall in intestinal tonus and inhibition of motility. Very soon afterward there was a rapid rise in tonus leading within several seconds to retching. Following the retching movement both tonus and motility returned to normal levels.

In dogs with two Thiry-Vella loops the same results were obtained from both loops when apomorphine was given. If only one loop was denervated the response was obtained from the innervated loop but not the denervated loop. The conclusion was that the response was of nervous reflex and resulted from excitation of central autonomic mechanisms. — Wm. D. Beamer.

GROSSMAN, M. B. AND IVY, A. C.: *Effect of alloxan upon external secretion of the pancreas.* (*Proc. Soc. Exp. Biol. Med.*, v. 63, p. 62, Oct., 1946.)

A standard secretin concentrate containing both secretin and pancreozymin was used on a series of dogs treated with alloxan. The alloxan dosage was 75 milligrams intravenously per kilogram body weight. In two normal dogs the threshold dose of the secretin for pancreatic secretion was 0.3 and 0.5 mg. respectively. In four dogs made diabetic by the alloxan injections the threshold dose was 2, 4, 5 and 10 mg. respectively. In two other alloxan-treated dogs that failed to become diabetic the threshold dose for secretin was 0.4 and 0.8 mg. The amylase concentrations of the pancreatic juice of the diabetic dogs receiving the secretin were within the range of the non-diabetic dogs.

The fact that alloxan causes vacuolization of intralobular duct cells but does not affect the acinar cells suggests that the intralobular cells are activated by secretin to secrete bicarbonate while the acinar cells are activated by pancreozymin to secrete enzymes. — J. Wauldron.

BOSE, A. N., GHOSH, J. K. AND RAKSHIT, P. C.: *The intestinal secretion of sulfanilylbenzamine in comparison with sulfanilamide, sulfathiazole and sulfaguanidine.* (*J. Pharmacy Pharmacol.*, v. 19, p. 1, March, 1946.)

Sulfanilylbenzamine, which has had some clinical success in the treatment of bacillary dysentery, and paradyntentery, and has also been shown to act synergistically

with the specific bacteriophage against *Vibrio cholera*, was studied from the standpoint of intestinal secretions. The drug was compared with other sulfonamide compounds. Guinea pigs were injected subcutaneously with the sulfonamide under consideration, and at times ranging from 2 to 4 hours the animals were sacrificed; the stomach, small intestine, cecum and large bowel were ligated and the segments washed. It was found that sulfanilylbenzamine was excreted in the cecum in greater concentrations than any other sulfonamide. Sulfathiazole was present in the small bowel in highest concentrations and sulfanilamide was just below sulfaguanidine in being secreted by the stomach. There is included a discussion of the various phases of bacillary dysentery. An explanation of the beneficial results with sulfanilylbenzamine in acute dysentery is advanced on the basis of the large amount of secretion of the drug from the cecum. It is suggested that penetration of the cecal tissue is more assured by a drug secreted by the cecum than by one of the poorer absorbed sulfonamides. — Wm. J. Snape.

ROCH E SILVA, M., SROGGIE, A. E., FEDLAR, E., AND JAGUES, L. B.: *Liberation of histamine and heparin by peptone from the isolated dog's liver.* (*Proc. Soc. Exp. Biol. Med.*, v. 64, p. 141, 1947.)

Since peptone in vivo produces a shock-like syndrome in the dog associated with discharge of histamine and heparin from the liver, but produces only very small amounts in the isolated liver when Tyrode's solution is used as the vehicle, the authors decided to try whole blood. Blood collected in silicone-treated vessels was used as the perfusing fluid. The amount of peptone used was 3 grams in 10 cc of saline and this was then added to 250 cc of whole blood. Observations were also made with heparinized blood, defibrinated blood and Tyrode's solution as the vehicle. The whole blood collected in silicone-treated vessels produced enormous amounts of histamine and heparin when perfused through the isolated liver and the greater part of these substances were liberated at the beginning of perfusion. Heparinized blood and defibrinated blood also produce significant amounts of heparin and histamine although there is some evidence that heparin offers some protection depending on the time it is in contact with the peptone before perfusion. From these experiments it is concluded that blood is necessary for the production of histamine and heparin. The fact that Tyrode's solution gives even small amounts of these substances is attributed to the fact that some blood remains in the liver. By noting the decrease in platelets and leucocytes after perfusion the authors suggest that they also participate in the production of histamine and heparin. — J. M. Waldron.

SEEBURG, V. P., ILLG, P. L., AND BROWN, D. J.: *The intestinal absorption of penicillin G.* (*Science*, v. 104, p. 342, Oct. 11, 1946.)

To obtain comparable serum concentrations and therapeutic effectiveness the oral dose of penicillin is about 4 to 5 times the parenteral dose. Only a minor

part of the loss is due to destruction of the penicillin by the acid gastric juice. The authors concluded from experiments on cats that the major portion of an oral dose of penicillin passes thru the upper intestinal tract without being absorbed. When the penicillin reaches the lower bowel it is destroyed by penicillinases present there. The destruction of penicillin in the bowel increases progressively downward. The authors therefore suggest that increase in efficiency of the oral method can be brought about only by increasing the penetrability of the penicillin thru the intestinal mucosa. — M. H. F. Friedman.

D. HOSKINS AND G. M. DACK.: *A study of chemotherapy in experimental dysentery of Macaca Mulatta with emphasis on clearing the carrier state.* (*J. Inf. Dis.*, v. 78, p. 32, 1946.)

The rhesus monkey (*Macaca Mullata*) was used by Hoskin and Dack to study bacillary dysentery because it is a known carrier of *Bacterium dysenteriae* (Flexner) and develops an acute illness clinically and pathologically comparable to that in man. Therapy of the carrier state with sulfaguanidine was difficult to interpret because the two known carriers and three additional monkeys of a group of 11, all treated with sulfaguanidine developed dysentery when placed on a vitamin deficient diet. Five of ten animals with acute dysentery improved on sulfaguanidine therapy while 5 others showed no improvement. Three of the animals failing to respond to the sulfaguanidine were shown to have developed a drug-fast strain. Except in one instance it was not possible to establish a known strain of *Bact. dysenteriae* by feeding it to 10 monkeys. It was also not possible to induce an acute illness by feeding to infected animals staphylococcal enterotoxin or *Psuedomonas pyocyanens*, a predominant organism found in monkey dysentery. — J. M. Waldron.

F. J. MOORE, J. F. KESSEL, D. G. SIMONSEN AND J. MARMORSTON.: *Experimental basis of sulfonamide therapy in bacillary dysentery.* (*J. Inf. Dis.*, v. 78 p. 25, 1946.)

In an effort to determine whether sulfonamides alter the activity of the toxins of dysentery bacillus Moore and co-workers treated mice with sulfaguanidine and sulfasuxidine both before and after injection of a sterile filtrate of Flexner strain of dysentery bacillus. The results of these experiments show that these drugs did not alter the action of the toxin and therefore probably do not act favorably on absorbed toxins in man. Since these drugs are clinically effective it must be due to direct action on bacteria in the lumen of the intestine. In vitro studies on synthetic medium showed sulfathiazole to be 25 times more active than sulfadiazine, 40 times more active than sulfaguanidine and 100 times more active than sulfasuxidine against *Salmonella-Shigella* organisms. However, it is the concentration of the drug in the lumen of the intestine that is effective as shown by above experiments. Studies on fecal concentration in man revealed that enteric-coated sulfadiazine produced a level 3 times that of

uncoated sulfadiazine and 14 times that of uncoated sulfathiazole. From the above experiments the following order of performance is given for sulfonamide compounds in the treatment of bacillary dysentery: enteric-coated sulfadiazine, enteric-coated sulfathiazole, sulfasuxidine, uncoated sulfadiazine, uncoated sulfathiazole and sulfaguanidine.—J. M. Waldron.

PATHOLOGY

DAVIS, J. E.: *Evidence that the hemolytic anemia caused by fat and choline is not due to lipotropic action.* (*Science*, v. 105, p. 43, Jan. 10, 1947.)

Feeding of a high fat diet together with choline causes rapid development of an acute hemolytic anemia, accompanied by a rise in the icterus index. Regression occurs following withdrawal of either the fat or the choline. While on the high-fat plus choline diet, two dogs (one splenectomized) were given daily doses of atropine. The erythrocyte count returned to normal in two days. A third dog, receiving fat plus choline but not atropine, remained anemic.

Davis thinks that choline has a pharmacologic action on the vascular system supplying the erythropoietic tissues; the vasodilation and improved blood and oxygen supply depressed erythropoiesis. The action of choline on the blood vessels was antagonized by atropine so that erythropoietic depression did not occur.—M. H. F. Friedman.

FRIESEN, S. R. AND WANGENSTEEN, O. H.: *Experimental burns accompanied by histamine administration abets the ulcer diathesis.* (*Proc. Soc. Exper. Biol. Med.*, v. 63, p. 345, Nov., 1946.)

Dogs and rabbits under sodium pentobarbital anesthesia were used. When the control animals were burned 40% by immersion in 100°C water for 10 minutes, only one out of 7 dogs developed minute-gastric bleeding ulcers in 6 days. All of the eight dogs receiving burns to the same extent but in addition also receiving histamine in beeswax developed ulcers in 5 days. In other series of experiments it was found that the more extensive the burn the more profound was the ulceration following histamine administration. The bleeding was more extensive in the burned dogs receiving histamine than in the untreated burned dogs. The conclusion was drawn that experimental burns abet the ulcer diathesis.—J. Wauldron.

DUFF, G. L., McMILLAN, G. C. AND WILSON, S. C.: *Hydropic changes in pancreatic ductules and islets in alloxan diabetes in the rabbit.* (*Proc. Soc. Exp. Biol. Med.*, v. 64, p. 251, 1947.)

Duff et al report the production of hydropic degeneration of both the ductules and islets of the pancreas of rabbits following alloxan diabetes of long duration. Fifty-three of fifty-six rabbits, each treated with protamine insulin and glucose for no more than 14 days after receiving intravenously 200 mg/kg of alloxan in 5% aqueous solution, became persistently diabetic. Those who were resistant to the diabetogenic

action of alloxan, together with control animals, were sacrificed at varying intervals up to a year. The earliest appearance of hydropic degeneration was 45 days after injection of alloxan and it was never absent after 90 days providing the average blood sugar level had been 303 mg per 100 cc during the experiment. However, there was no correlation between the degree of hydropic change. The hydropic changes in the islets persisted for periods up to a year without evidence of histological degeneration in contrast to the dog and cat. The alpha cells remained normal but appeared to increase in number. Preliminary observations showed that adequate insulin treatment will reverse the hydropic change of both the ductules and islets. Furthermore, the regenerated islets cells with full granular cytoplasm are indistinguishable histologically from normal beta cells.—J. W. Waldron.

OKEY, R.: *Biotin and avidin intake and liver cholesterol.* (*J. Biol. Chem.*, v. 165, p. 383, 1946)

Guinea pigs and rats were fed measured amounts of cholesterol and given diets either rich or poor in biotin. Guinea pigs on an avidin-containing diet (whole egg) had only about 50 per cent of the liver lipids found in the other guinea pigs, while the addition of 2 gammas of biotin daily to diets low in biotin increased the liver cholesterol values by about 100 per cent.

Rats on low biotin diets stored little cholesterol in their livers even though their cholesterol intake was high. Addition of biotin to the diet or removal of avidin from the diet increased the liver cholesterol. The experiments showed that biotin is essential for deposition of cholesterol in the liver and that avidin both prevents deposition of cholesterol and removes cholesterol from the liver.—B. R. Adolph, Jr.

METABOLISM AND NUTRITION

SHANE, S. J. AND DEYKE, V. F.: *Observations on the sprue syndrome.* (*Canad. Med. Assoc. J.*, v. 55, p. 448, 1946.)

The diagnostic criteria of the sprue syndrome are: 1. steatorrhea (always present), 2. wasting (always present), 3. flat glucose tolerance curve (almost always), 4. macrocytic anemia (relatively constant finding), 5. hypochlorhydria (very frequently but not always present), 6. radiologic evidence of disturbed small bowel pattern, and 7. excess total fat (but normal fatty acids) in feces.

The chronic diarrhea with resultant faulty fat absorption and disturbed bowel pattern which is frequently seen may perhaps be recognized as "secondary" sprue when hematopoietic derangement is absent. Ultimately the case of "secondary" sprue may become a case of "primary" sprue.

Therapy is aimed at restoring nutritional deficiencies. High protein-carbohydrate diet is essential, fat is not. Parenteral feeding may be necessary where absorption is very much impaired. With improvement in bowel function, fat may be added to the diet in gradual stages.

Adequate liver extract administration is important for both the gastrointestinal condition and the hematologic picture. Parenteral administration of the fat soluble vitamins A, D, and K is necessary. — F. X. Chockley.

SPIES, T. D. AND COLLINS, H. S.: *Observations on aging in nutritionally deficient persons.* (*J. Gerontol.*, v. 1, p. 33, 1946.)

Various conditions brought on by lack of proper nutrition have been variously judged to be simply a part of growing old, or to have an effect of making a person appear old beyond his years. This is particularly evident in the southern United States. As a result of a study made over a period of ten years at the nutrition clinic, Birmingham, Alabama, it was found that nutritional deficiency is most common among women of child-bearing age. These women frequently have inadequate diets during pregnancy and as a result both mother and child are affected.

Of the cases observed at the clinic, most of the women suffered from pellagra, nervousness and hallucinations, sore mouth and tongue, severe pains in the feet and legs, and loss of weight. One woman of 30 was judged by her appearance to be 50. Another who was 70 began again to lead a vigorous and happy life after proper diet and treatment were prescribed. No one knows what role nutritive failure plays in the aging process, but a greater effort should be made to apply what we do know so that older people suffering from lack of proper nutrition may be returned to an active and happy life. — Courtesy Psychosomatic Medicine.

MISCELLANEOUS

ANDERSON, A. B.: *Lead content of urinary calculi and bile.* (*Biochem J.*, v. 39, p. 58, 1945.)

Urinary calculi were found to contain widely ranging amounts of lead, similar to those in long bones: from 1.3 to 29.0 milligrams per 100 grams. The lead content of gall-stones was found to range from 0.3 to 65 milligrams per 100 grams, the higher values occurring in pigment stones. The gall-bladder bile taken post-mortem had a lead content of 8 to 97 micrograms per 100 milligrams bile and was within the range of lead concentrations found in blood. — F. E. St. George.

HERFORD, K.: *Treatment of Peptic Ulcers with Nicotinic Acid.* (*Casopis Lekaru Ceskych*, v. 85, No. 36, p. 1244-1249, 1946.)

Two hundred and eight cases of gastric or duodenal ulcer were treated with daily administration of 5 c.c. of a 1% solution of nicotinic acid chloride. This treatment was very successful in 52% of the cases, while in 10% only some relief was achieved; in 17% the treatment had to be stopped because of pancreatic pain and, in 11% no improvement was seen. Transitory reactions, as flushing of the face, were not considered a contra-indication for further treatment. Cases with a tendency to bleeding were not treated with this method. — O. Felsenfeld.

VAHALA, Z.: *A Case of Pneumatosis Cystoides of the Intestine.* (*Casopis Lekaru Ceskych*, v. 85, No. 36, p. 1257-1259, 1946.)

"Pneumatosis cystoides intestini" consists of the formation of small cysts in the lymph spaces. About 150 cases were described to date. Author observed a patient with this condition who was operated because the cystic pneumatosis pretended appendicitis. — O. Felsenfeld.

PROCHAZKA, V.: *Perforated Paratyphoid Circumscribed Peritonitis in Pregnancy.* (*Casopis Lekaru Ceskych*, v. 85, No. 39, p. 1366-1369, 1946.)

Eighty-two cases died of salmonellosis in Prague, Czechoslovakia, between 1934 and 1943. Of the 75 who died of *E. typhosa* infection, 3 had perforations of the gall bladder. Among 7 cases of *S. paratyphi B* none had perforations of the gall bladder or of the intestines. Author described a case of paratyphoid B infection in a 38-year-old woman during the eighth month of pregnancy. She had gall bladder stones. A perforation occurred with circumscribed peritonitis. The operation saved the life of the patient but the child was born dead. The bile showed only *S. paratyphi B* organisms. — O. Felsenfeld.

SÍPEK, O.: *Intestinal Actinomycosis Treated with Penicillin.* (*Lekarske Listy*, v. 1, No. 14, p. 335-338, 1946.)

Two cases were described. Complete cure was achieved in one of them, while the second, probably because of the extensive secondary infection, did not show a good response. — O. Felsenfeld.

BIRGUS, J.: *Rare Complication of Appendicitis in Puerperium.* (*Lekarske Listy*, v. 1, No. 21, p. 510-512, 1946.)

The appendix was pressed against the promontory during birth and perforated. Abscess formation with destruction of the 4th and 5th lumbar vertebrae ensued. The condition was not recognized because of the lack of clinical symptoms during life. Only fever was present which did not react to sulfa drugs or penicillin. — O. Felsenfeld.

KLEINFELDER, EDMUND.: *Significance of calcification for the roentgen diagnosis of aneurysm of the abdominal aorta.* (*Radiology* 47, 3, 597, Dec. 1946.)

Abdominal aneurysms are becoming more frequent but are overlooked in 80% of the cases, largely because their calcification is confused with that of the common calcified aorta. In order to avoid this confusion, attention is called to the distinguishing characteristics of the calcifications of the abdominal aorta. In aneurysms only a portion of the aneurysm wall is outlined on the film by a single curved, continuous or broken, line of calcification, while a considerable portion of the wall

is ill-defined because of their indistinct calcifications. This requires very close inspection and multiple films have to be taken in various projections. Such a unilateral distinct line, often sharply curved, is most readily confused with a calcified tortuous aorta.

A case of ruptured aneurysm of the abdominal aorta is reported in which the characteristic calcification was associated with a filling defect of the rectum.—Franz J. Lust.

BROWN, SAMUEL AND HAPER, FOREST G.: *Roentgen diagnosis of duodenal ulcer in the right lateral decubitus position.* (*Radiology* 47, 6, 575, Dec. 1946.)

The authors draw attention that the fluoroscopic and roentgenographic study of the patient in right lateral horizontal position has proved to be useful in arriving at a more accurate knowledge of the condition of the duodenum than can be obtained from the frontal projection alone. The fundamental principles underlying this technic are sound and the procedure can be carried out without the complicated devices which have been introduced for the demonstration of gastroduodenal lesions. The authors illustrate the result of this very widespread adopted technic by many fine illustrations, in which the posterior-anterior roentgenograms were apparently normal, whereas those in the aforementioned position revealed a duodenal ulcer.—Franz J. Lust.

OULD, CARLTON L. AND DAILEY, MORRIS E.: *Simultaneous radiographic and gastroscopic examination of the stomach.* (*Radiology* 48, 1, 8, Jan. 1947.)

The appearance of the gastric mucosa was studied by means of simultaneous radiographic and gastroscopic examination. A contrast medium composed of equal parts of diodrast and a saturated aqueous solution of methyl cellulose was found to be satisfactory for mucosal relief studies. The author suggests that the zones visualizable at gastroscopy could be increased by a slight change in the instrument. If the source of light were not separated from the objective, the angle of vision and the cone of light would more nicely coincide. This would make it possible to see more of the posterior wall of the stomach. The new omni-angle gastroscope, by allowing the angulation of the objective to be shifted at will during an examination, has somewhat reduced the extent of the area hidden behind the angulus and near the cardia.

The methyl-diodrast mixture, with the usual relief methods, gave satisfactory results. Since the medium does not distort the stomach by its weight, a complete investigation of the limitation of gastric mobility in disease may be very profitable. This method would have real clinical value if, thereby, radiologists could

inform the surgeon that a pathologic process had extended beyond the stomach.—Franz J. Lust.

GLADSTONE, R.: *Nausea and vomiting of pregnancy—a study in psychosomatic and social medicine.* (*Lancet*, v. 251, p. 336, Sept. 7, 1946.)

The author has made a clinical and statistical investigation of the nausea and vomiting of pregnancy. This shows that the syndrome may be the physiological expression of an underlying emotional state which may be equated with that of disgust. Relevant etiological characteristics of the personality are disturbed coital function, undue mother attachment, and previous dyspepsia. Relevant factors in the life situation are the frequency of undesired coitus and the physical proximity of the mother.

The author concluded the need to supplement physical examinations with investigation into the emotions and life situation of the expectant mother.—Joseph Medoff.

FOSTER, D. BERNARD.: *Degeneration of peripheral nerves in pernicious anemia.* (*Arch. Neurol. Psychiat.*, v. 54, p. 102, 1945.)

Applying the usual neuropathologic staining techniques, Foster examined the spinal cord, posterior root ganglia and peripheral nerves in 5 cases of pernicious anemia. The blood values were normal in two patients who had received liver therapy, while the other three were in severe hematologic relapse. In all cases there was histologic evidence of peripheral nerve degeneration, but the patient in hematologic relapse showed more severe damage in their peripheral nerves. The author suggests that certain manifestations of the disease are due to changes in the peripheral nerves, and that the regenerative capacity of peripheral nerves is such that adequate liver therapy will effect improvement in the neuritic component of the affliction.—Courtesy Biological Abstracts.

FRISCH, A. W. AND QUILLIGAN, J. J. JR.: *(Modified cephalin cholesterol test (Hanger) in the study of hepatic disease.* (*Am. J. Med. Sci.*, v. 212, p. 143, 1946.)

A simple process for preparing the antigen for the test is described. The cephalin cholesterol antigen mixture is more opalescent than that described by Hanger and the mixture with serum results in a granular precipitate rather than flocculation. However false positives resulting from either exposure of the serum to light or from aging are not obtained. Interpretation of the flocculation pattern can be made more accurately than hitherto when using Hanger's original cephalin-cholesterol preparation.—G. Klenner.

The Irritable Colon, Its Recognition and Management

By

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THE PATIENT who relates to his doctor a long, complicated, and at times seemingly contradictory story of intestinal irregularity, presents a diagnostic problem the difficulty of which soon becomes all too apparent to the listener. The patient usually has had his symptoms for a period of time long enough for him to study his condition, and he has made mental notes of the peculiarities of some or of all of the symptoms which bother him. He has noticed the occurrence of diarrhea and the time of day it appears, and what it follows in the way of food, exercise, or mental state. He may have observed that spells of diarrhea alternate with spells of constipation, and cannot understand why there should be periods during which there are many soft and liquid stools and then periods of constipation, with stools now being in the form of hard pellets. The presence or absence of mucus or blood in the stool, abdominal cramps or actual pain have all been entered in his mental log. He has noted that these may appear singly, or at times various symptoms will team up together to broaden the symptom picture and make his disease yet more complex for him. His self-study has enabled him to go into considerable detail in giving his history to the physician, and the latter soon finds himself swamped with the multitude and variety of the patient's complaints. In getting the history, while the physician's patience may be taxed to the utmost by the recital, still it is necessary to hear out the patient, for all his symptoms must be considered in evaluating the condition, and often valuable clues are given which would indicate the lines definitive investigation should take. The real problem is accurate evaluation of the important points in the history and deciding whether or not there are present serious organic lesions in the intestinal tract.

If one is present, it must be discovered and eradicated. If one is not present, the patient still demands relief from his very annoying and often incapacitating symptoms. A careful and thorough physical examination is indispensable, for the diagnosis of Irritable Colon must be considered only after one is sure that no other lesion is present. I agree with other writers that this diagnosis is made by exclusion, but this paper will describe physical findings that aid in the establishment of the diagnosis of Irritable Colon, after the presence of other lesions have been excluded.

The name "Irritable Colon" seems to me to be the most apt of the many names that have been suggested for this functional disease of the colon. It is not a colitis, so the names which apply the word "colitis" to this condition such as 'spastic colitis', 'mucous colitis', 'simple colitis', 'catarrhal colitis', 'muco-membranous

colitis', 'fermentative colitis', and 'toxic colitis' imply an inflammatory condition of the colon which is not present, and they convey a false connotation of a disease process being present. The patient is apt to minimize or forget the modifying adjective and remember only the fact that his condition was called some kind of a "colitis". The term 'Irritable Colon' indicates both the functional nature of the condition, and the seat of its major expression. In Irritable Colon there is absence of colitis and presence of its symptoms. (1)

The functional predisposition may be found in fatigue, anxiety, or failure or inability to relax. (2) When this is acted upon by heredity, fear of disease, actual systemic disease, the use of laxatives, food allergy, environment, and irregular habits—as these factors act upon the already present anxiety state and fatigue, the symptoms develop.

The colon is controlled by two sets of nerves, the sympathetic and the parasympathetic. They have opposite influences on the functions of the colon, and they should be in a state of fine balance to control properly its physiology. As one set acquires abnormal sensitivity to stimulation, or as it receives abnormally heavy stimuli, the colon is unduly influenced by that set, and symptoms of imbalance become apparent. The nerves control motility, secretion, and absorption, and other functions of the colon, and also there are present nerves which carry visceral sensory impulses. One can see, then, that if one set of nerves were in command, at least four functions of the colon would be affected. Increase in motility speeds along the passage of colonic contents. Increased secretion of mucus creates additional bulk of a moist nature and this is added to the semi-fluid material that is already present. Retarded absorption also makes for increased fluid bulk. All this helps to account for the number and fluid consistency of the bowel movements. At the same time, the patient becomes aware of his colon by way of increased sensitivity to visceral-sensory stimuli. In addition to these broad functions of the colon, it excretes heavy minerals and substances that have been absorbed higher up, (3) and detoxifies disease-producing bacteria.

It is easy to see then that considerable disturbance in abdominal physiology will follow abnormal irritation of the colon, and that the history given in cases of this kind will be found to be lengthy and detailed.

While these several factors enter into the production of irritable colon, the symptoms usually follow a fairly characteristic pattern. In those cases in which diarrhea predominates, the diarrhea usually occurs in the morning, and the patient will state that he has from three to

six or more bowel movements before noon. He has one or two on getting up, perhaps another before breakfast, and immediately after breakfast he has another one or two. After this there may be one to several more before the colon quiets for the day. This quietude will be blasted by emotional upsets and evacuations will be resumed while nervous tension is maintained. The movements are soft, or mushy, or liquid, with mucus becoming more prominent as the stools increase in number. A symptom pattern like this exemplifies the working of the 'gastro-colic reflex'. (4) Many things may start the reflex. The taking of food into the stomach at breakfast, or even the taking of a glass of water on getting up may be sufficient, and the patient will have a prompt bowel movement. Either on purpose or unwittingly one may train the reflex to respond to stimuli other than the actual taking of food into the stomach. The anticipation of that act may start the reflex. Sometimes the reflex has been conditioned to respond to hot water applied to the face as the first step of shaving. Rush waves which are normally weakened and lost as they travel down the intestinal tract are perpetuated by the sensitive nerves and irritable musculature, and result in an evacuation.

Patients at times will notice periods of diarrhea alternating with periods of constipation. The diarrhea is similar to what has already been described, but when they are constipated they notice that the stools are hard and often in the form of pellets. This indicates another form of abnormality of muscular action of the colon, in that spasticity of the muscles in the lower colon retains the fecal material in the bowel and subjects it to pressure and segmentation. The absorptive function for the time being is increased, and the stool is hard and dry.

The diagnosis of Irritable Colon, as has been already stated, is made by both exclusion and establishment, and after getting the salient parts of the history well in mind, the examination must be thorough. There is little if any excuse for missing a serious lesion of the lower colon in these cases that give such a long history which point so definitely to this region. It is well to suspect the presence of carcinoma in the colon until its absence is determined. If there is history of blood in stools there is no excuse for failing to search for carcinoma, for there is an aphorism to which I subscribe that the presence of blood indicates carcinoma until the latter is proved absent. Palpation of the abdomen will often reveal tenderness over the sigmoid, the splenic flexure, and the cecum. The sigmoid is usually a firm roll under the examining fingers. The cecum will probably give a tympanic note on percussion. The examination should include procto-sigmoidoscopy and X-ray examination by means of a barium enema.

Various findings in the colonic shadow as cast on the film have been reported, but none I consider to be indicative of irritable colon only. The most common finding is loss of haustral markings in the descending and sigmoid colon without much if any loss in caliber of the lumen. Many cases of frank irritable colon will show a normal outline of this region. Intestinal parasites

must be found if they are present. *Eutameba histolytica* may produce symptoms resembling irritable colon especially if they are present in subclinical numbers. (5) Absent or low free gastric acidity may be the cause of gastrogenous diarrhea. (6) Having obtained normal findings in gastric analysis, stool examinations and cultures, barium enema study being inconclusive, and procto-sigmoidoscopic examination showing no tumor or specific ulcerations, there is a procto-scope finding which I consider to be diagnostic of irritable colon. The normal rectal ampulla, when viewed through the proctoscope, shows a mucosa which is pale, grey or parchment white in color in which the blood vessel pattern is readily seen and stands out as red, branching, interlacing lines. In colitis the vascular pattern is accentuated, more pronounced, and the finer vascular branches are seen. The background of grey or white membrane can still be seen, except in the most pronounced cases of colitis. These latter cases usually show other lesions which make confusion with irritable colon impossible. In irritable colon the vascular markings are lost in a background of blushed or salmon-colored mucosa which at times may also be granular. This sign was first pointed out to me by Dr. Henry A. Monat, when he was chief of the Gastro-Enterological Service to which I was attached. The loss of blood vessel markings, which I consider to be diagnostic of irritable colon, may be partial or complete. The entire visible lower rectal segment may show this change or there may be only patches here and there where the vascular pattern is lost. Associated with this appearance of the mucosa, there usually is noted the presence of strings or globes of thick, glary white, or translucent mucus, which may be festooned from one side of the wall to another. The appearance of the mucosa in these three conditions—the normal colitis and irritable colon—can be described graphically by comparing them with the appearance of a leafless tree in the winter-time. The tree with its branches and limbs silhouetted against the dull, grey winter sky resembles the normal appearance of the vascular pattern in the rectum. After a heavy fall of fluffy snow the pattern of the limbs and branches becomes more pronounced and even the smaller twigs can easily be seen. This is the appearance of the mucosa in colitis, with congestion of the blood vessels being apparent. Going back to the naked tree, dusk sets in and the tree is lost entirely in a grey enveloping fog so that its limbs and branches are no longer seen against the homogeneous background. This is the impression one gets in looking at the irritable colon, that the mucosal background has enveloped the vascular marking in an all-suffusing blush. When this is seen in an otherwise normal colon, either in the entire recto-sigmoid or in patches, the diagnosis of irritable colon is warranted.

The treatment is not as simple as it may at first appear. One might expect, since this is a functional disease based on anxiety or nervousness of some sort, that after the anxiety has been relieved or the fatigue corrected, the colon would spontaneously return to normal. This may happen eventually without any further treatment,

but one can speed recovery, shorten the convalescent time, and expedite a favorable outcome by additional therapeutic measures. The patient is helped with his anxiety, he is put to bed to recover from his fatigue,

establishing the normal acid pH of the colon would help to eliminate the putrefying and proteolytic organisms which perpetuate intra-colonic irritation. For a long time the importance to the colon of the acidophilus

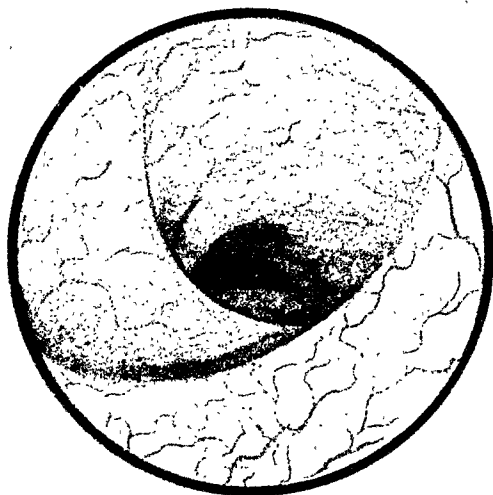


Fig. 1 NORMAL COLON

Mucosa grey and blood vessel pattern readily seen.

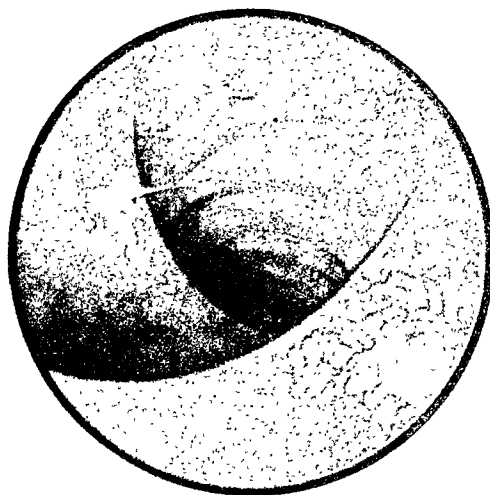


Fig. 3 IRRITABLE COLON

Blood vessel markings lost in blushed mucosa, with granular surface and excess mucus.

and he is given mild sedatives to relax overtaut nerves. Gastric anacidity if present is counteracted by administration of hydrochloric acid. He is put on a bland, pureed diet, and irritants to the gastro-intestinal tract are withheld. These are general measures and influence the colon only indirectly, by removal of the abnormal

bacillus has been recognized, and acidophilus milk and acidophilic cultures have been recommended in the attempt to re-implant in the colon a self-perpetuating flora of this organism.(7)

Lactic acid has also been given to lower the pH of the colon, trying to provide a suitable acid medium for the growth of the acidophilic bacteria. It has been shown that lactic acid provides both the pH desired and also a somewhat specific effect on potentially pathogenic organisms especially streptococcus viridens, the ameba, and trichomonad. (8) Lactic acid inhibits the activity of amylase which is essential to their growth, and they die.(9) Lactic acid given by mouth is slowly absorbed in the small intestine so that in the colon there is a relatively low concentration of it present.(10) Kessel (11) has shown that lactic acid produced an average reduction in colonic pH from 7.2 to 6.5. As for the antibiotic action of lactic acid upon protozoa, Sokoloff (9) has shown that lactic acid even in a weak solution of 1-1000 impedes the multiplication of free-living protozoa including amebae. He also found that lactic acid was efficient even when the pH of the solution was raised to 7.0.

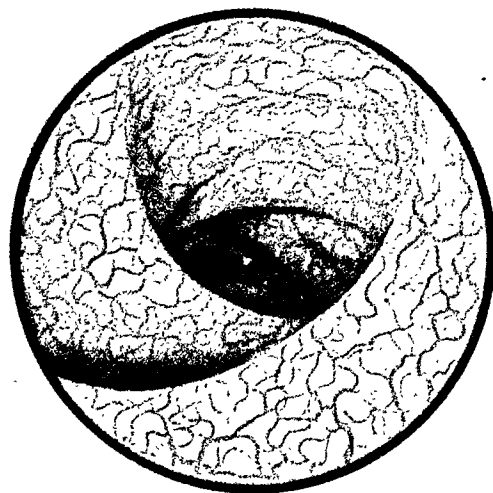


Fig. 2 COLITIS

Blood vessel pattern accentuated, but grey background still present.

nerve stimulation and by providing a non-irritating diet. The local pathological state of the colon also requires attention.

Diarrhea alters the colonic mucosa in such a way as to inhibit the growth of the acidophilic and fermentative type of bacteria and favor the growth of proteolytic and putrefactive organisms. This interferes with the absorption and detoxifying functions of the colon. Re-

Polymolecular lactic acid crystals combined with lactose is found to liberate lactic acid slowly as it descends the intestinal tract and by the time it reaches the colon, lactic acid is present in effective concentration.(9) The preparation of polymolecular lactic acid and lactose used in my cases of irritable colon was Trilactic.* It was given in tablespoonful doses three times a day with meals, for a period of about three weeks. It was found that the majority of cases so treated began to show symptomatic improvement in the first week as evidenced

*Manufactured by Professional Laboratories, New York.

by reduction in the number of stools per day, and in the amount of mucus passed with each stool. Proctoscopic examination at this time usually showed return of vascular markings in the mucosa and loss of the thick, glary mucus. Treatment is continued for a total period of three weeks even if clinical relief appears earlier than this, to insure the adequate regrowth of acidophilic organisms. During the first five days of treatment some patients may complain of increased quantity of gas in the colon but this disappears as treatment continues. In severe cases the dose may be doubled. After an initial treatment period of three weeks, Trilactic is withheld for a week or two. If symptoms return, a second course is started.

My cases comprise a total of several hundred occurring in service age personnel seen in the Gastro-Enterological Service of a large Naval Hospital. Since the patients were largely in the younger age group, it is possible that the condition of irritable colon had not been present long enough to have produced widespread and advanced changes in colonic physiology and pathology. However, the symptoms were severe enough to require investigation and relief. My cases had usually a very definite nervous factor in the etiology since they were all subject to active duty in combat areas with all the nervous tension that duty entails, or selection for such future duty. With the cessation of hostilities and the widespread shrinking of naval activities the element of anxiety was removed. In some cases of long standing seen in the last half of 1945 the irritable colon habit was deeply ingrained and these men had to have psychiatric assistance to eradicate the nervous component. Ordinarily, however, this was not necessary.

At first when the diagnosis of irritable colon was made the patient was put on a course of sulfasuxidine and sulfadiazine, and was given histamine desensitization. The results were not good. The cases that improved could be put in the class of those who would have improved spontaneously with the removal of the nervous and alimentary factors. But this treatment was not beneficial in a satisfactory proportion of cases. Trilactic was added to this and results were much better. Then histamine desensitization was dropped and finally the sulfa drug. Now the routine is that the patients get only Trilactic unless there is indication for additional specific therapy.

Many of the cases seen were those having some other GI lesion such as duodenal ulcer. Here the primary attention was given to that lesion for two reasons. First, since it was felt that irritable colon in these cases may

be due to the irritation of the ulcer, it was not to be expected that the colon would improve until the ulcer became quiescent. Second, the symptoms of ulcer, pain and at times hemorrhage, overshadowed in importance the symptoms of irritable colon and required prompt relief. Those cases of uncomplicated irritable colon without psychiatric fixation responded promptly to treatment.

All cases were given a complete GI work-up. On admission they were put on a meat free diet and after 4 days a stool specimen was examined for the presence of occult blood, ova, and parasites. They were then put on an ulcer No. 2 diet, consisting of bland, pureed food. Proctoscopic examination was done and a rectal smear examined. On excluding other diseases and establishing the diagnosis of irritable colon, Trilactic was started and the bland diet continued. Sedatives were administered as necessary — usually phenobarbital gr. $\frac{1}{4}$ three or four times a day.

A gastric analysis was done, and then a GI X-ray examination and a barium enema study. Proctosigmoidoscopy was repeated in ten to fourteen days and if improvement was not satisfactory, further studies were done and the dose of Trilactic increased. Stool culture was grown to determine the predominating organism and if in the history symptoms were given which made one suspicious of a previous infection with an organism of the paratyphoid group, this was checked with an agglutination titre. Other investigations were done as indicated in an effort to run down the persistent causative agent. If it was deemed desirable from an appraisal of his personality make-up, a psychiatric opinion was obtained. Frank psychiatric cases received treatment from that department. With this management a large proportion of my cases were able to resume duty or be separated from the service on points within a short time. They were cautioned about the possibility of recurrence if they again allowed themselves to become fatigued, or nervously overwrought, or if they resumed habits or dietary indiscretions inimicable to the colon.

SUMMARY

1. Irritable colon is a disease entity having its basis in some unusual nervous disturbance to which is added some local irritation. 2. The proctoscopic appearance of the mucosa is characteristic. 3. Treatment is directed toward the neurogenic factor and toward the colon. The former attempts to re-establish the normal nerve balance to the colon, and the latter to restore the normally low pH of the colon.

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The Role of Vitamin Therapy in the Management of Diabetes Mellitus

By

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IN ALL probability vitamin deficiencies cannot be considered to be causative factors in diabetes mellitus. However, some of the B factors (thiamine, riboflavin, and niacin) are essential to the enzyme systems which provide the normal mechanism for the utilization of carbohydrates. (1) Because of this relationship, it was predicted, and later demonstrated, that deficiencies in the B-complex exaggerate the severity of diabetes in experimental animals (2). Additional evidence of the importance of the B-complex to carbohydrate metabolism in the diabetic is found in the case histories of diabetic patients with concomitant vitamin deficiency symptoms. These case histories show convincing proof that supplementary therapy with vitamin concentrates produces definite and lasting amelioration of the severity of the diabetes (3). However, these findings should not be regarded as proof that vitamin deficiencies are causative factors in diabetes.

Repeated attempts to treat diabetics routinely by administration of large doses of water-soluble vitamins have been disappointing (4). In my own experience, over a 25-year period in Wisconsin, the occurrence of vitamin deficiency syndromes concomitantly with diabetes has been infrequent. Perhaps the greater frequency with which this combination of syndromes has been observed in clinics in Boston (5) and New York (3) is the result of fundamental differences in the economic, racial, and traditional dietetic backgrounds of the patient groups involved. If this is the correct explanation, it is reasonable to suppose that the non-diabetic group of patients in Boston and New York would show a higher incidence of vitamin deficiency than the non-diabetic patients in Wisconsin.

But more important than the etiologic questions discussed is the consideration of vitamin and mineral needs when planning the diet regimen for a diabetic. It is not surprising that the necessity of supplying an adequate vitamin and mineral intake has sometimes been overlooked since the emphasis has usually been placed on the restriction of glucose, provision for adequate supplies of protein and calories, avoidance of ketosis and satisfying the appetite of the patient. Certain general principles, other than the routine check concerned with the vitamin content of the foods to be included in the diet, should be followed to insure proper vitamin and mineral intake (6).

At present almost all diabetic dietary regimens prescribe some restriction of the caloric intake. This restriction of itself tends to reduce the requirement of

some of the water-soluble vitamins and thereby somewhat lessens the problem. In addition the limitation of the total preformed carbohydrate by means of larger proportions of fats in the diet further reduces the need for the B vitamins (7). This desirable effect of high-fat diet may be significant in the management of diabetes but it is seldom mentioned or taken into consideration. The provision of liberal amounts of meat in diabetic diets tends to assure adequate supplies of the B factors; however, under unusual conditions such as the recent period of meat rationing, this source of B vitamins may become undependable. Dairy products provide vitamin A and, if fortified milk is used, vitamin D. The universal tendency of the past two decades has been to emphasize the use of fresh fruits and juicy vegetables—especially those classified as containing 3, 6 or 9% carbohydrate. This practice provides vitamin C (ascorbic acid) and to some extent, vitamin A. Thus it is apparent that a dietary regimen can be planned which meets the criteria of any one of the various schemes for the management of diabetes and which at the same time provides the necessary vitamins in the foods themselves. The vitamin which is most likely to be critically deficient is vitamin D.

If the physician is faced with problems such as undependable co-operation on the part of the patient, limitations (economic or otherwise) in the availability of certain types of foods, or the need for restricting certain classes of food, vitamin concentrates can be prescribed. Such administration of vitamin supplements in the usual dosages will in all probability have no deleterious effect on the course of the diabetes. If a diabetic patient when seen for the first time shows evidence of avitaminosis, he should be given high-potency vitamin preparations suited to the deficiency picture he presents until the symptoms of the deficiency disappear. Under such circumstances multi-vitamin preparations are usually the wisest choice since deficiencies of single vitamins rarely occur (8).

If vitamin deficiency is not causative factor in diabetes, can diabetes bring about avitaminotic states? Does diabetes mellitus bring about an increase in the requirement of any of the vitamins? No tangible evidence has been reported that would indicate an increased need for any of the vitamins in diabetic persons. Their requirements are to all appearances the same as those of a non-diabetic's of similar size on comparable diets. Diuresis of itself is not thought to be responsible for any increase in the excretion and loss of water-soluble vitamins (9). Recent reports (10, 11) have discounted the theory that there is an impairment in the metabolic formation of vitamin A from carotene (12) in diabetics.

However, there are a number of complicating circumstances which make accessory vitamin intake valuable to the diabetic. It has been reported that striking decreases in the blood levels of vitamin A occur in diabetics as a result of acidosis and coma, acute or chronic infections, or sudden transfer to a low-fat intake (11). It has also been observed in non-diabetics that severe injury, infections and hemorrhage tend to produce low blood and urine levels of the water-soluble vitamins (13). Prolonged sulfonamide therapy may increase the need for B vitamins because of reduced synthesis of these vitamins in the intestinal tract (14). This has recently been shown to be true also for vitamin K. Supportive vitamin therapy is therefore important in the clinical management of patients with diabetic acidosis with or without coma, complicating infections, and those undergoing surgical measures. In such instances large doses of multi-vitamin concentrates appear to be the prescription of choice.

The group of older diabetics, which is growing increasingly larger as a result of the use of dietary measures and insulin therapy over the past 25 years, presents an additional problem since there is some evidence that aged persons have special vitamin requirements (15). Whether this change in vitamin needs is caused by decreased food intake, decreased absorption of certain foods, or other changes in the physiologic processes as a result of senescence is not yet clear; however, the practice of fortifying the diet of older patients with vitamin concentrates has much to recommend it to the cautious clinician.

In untreated or poorly managed diabetics, enlargement of the liver frequently occurs. A more rigid control of the diabetes and a generous protein intake, which is adequate for the metabolic needs of the liver, will help the liver to return to normal. In addition, vitamin A and the B-complex are important (4). Since the liver occupies a key position in carbohydrate metabolism (10), it is obviously essential that the best possible liver function be maintained in the diabetic. In patients with impaired liver function, large doses of vitamins should be given until the hepatomegaly has been reduced. The same therapy is, of course, indicated when any form of hepatic disease occurs either in diabetics or non-diabetics.

When parenteral feedings are required in the treatment of diabetics, it is generally assumed that only water, salt, glucose, and insulin are of vital importance. This is true if the diabetic patient has been adequately

nourished prior to the time when the need arose for the parenteral feedings and if there is to be a return to oral feedings within two to four days. If however, there has been a prior depletion, an acute or severe chronic infection, a severe and shocking injury, or if there is a prospect of prolonged parenteral feeding necessitated by surgical intervention in the gastro-intestinal tract, it may be desirable to include proteolytic digests and water-soluble vitamins into the parenteral fluids. Recent developments in the manufacture of such preparations have made this a safe procedure. An increase in the amino acid and vitamin intake may not only help to avoid edema, but may also result in a shorter convalescent period.

Under the present methods of management of diabetes, successful pregnancies in diabetic women are becoming more and more frequent. In the management of these patients, it should not be forgotten that there is a greatly augmented need for vitamins during pregnancy and lactation (18).

The occurrence of neurologic complications and various signs of vitamin deficiency disorders in diabetics has led some investigators to believe that nutritional inadequacy is the principal causative factor in these distressing complications of diabetes (5). On the other hand, the poor results from intensive vitamin therapy recently reported (19) have been duplicated in the experience of many of us. It should also be noted that dietary inadequacies may occur in diabetics as well as non-diabetics. But also since inadequately controlled diabetes has a definite effect on the neurologic disturbances (20), too much cannot be expected of intensive and prolonged administration of the B vitamins in diabetics with neurologic complications. If maximum results are to be obtained, vitamin therapy must be accompanied by the best possible management of the diabetes and attention to circulatory handicaps. It is also essential that thiamine administration be continued for several months although the dosage need not be large.

In summary, it can be said that although diabetes mellitus does not cause vitamin deficiency, and vitamin deficiency does not cause diabetes, there are nevertheless numerous complicating conditions which may occur in diabetic patients and which make it advisable to prescribe vitamin supplements. In the majority of these conditions, multi-vitamin preparations are to be preferred since they provide the greatest assurance of adequate vitamin therapy.

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Spontaneous Hyperinsulinism (Harris' Syndrome) A Survey of Twenty Eight Cases

By

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IT HAS become a time honored custom in the medical profession to perpetuate the names of physicians by connecting them with the syndromes they first described. This is a good tradition as it not only simplifies terminology, it also pays the respect that is due the author.

This writer suggests to introduce the term "Harris' Syndrome" for the clinical picture of spontaneous hyper-insulinism.

Doctor Seale Harris of Birmingham, Alabama, born in 1870, graduated from the University of Virginia in 1894. Fellow of the American College of Physicians, he addressed the American Medical Association at its convention in 1924 with a paper titled "Hyperinsulinism and Dysinsulinism" (1). Here are a few paragraphs of this paper. "... It seems probable that there are other dysfunctions of the islands of Langerhans, besides hypoinsulinism (i. e. diabetes mellitus), and that an excessive formation of insulin may occur. ... It also seems probable that a deficiency of the secretion of insulin may follow prolonged excessive work of the islands of Langerhans.

"It was this line of reasoning that caused me to think that there may be such a condition as hyperinsulinism, and when I saw the insulin reaction in diabetic patients, I realized that I had seen many non-diabetic patients who had complained of the same symptoms. ...

"We have not been able to find any reference to hyper-

insulinism in any medical publication. . . . Hyperinsulinism is a condition, perhaps a disease entity, with definite symptoms; i. e. those described as being due to hypoglycemia. . . . It seems possible that hypoadrenalism may be associated with hyperinsulinism. It also seems probable that secretory disorders of the islands of Langerhans may be associated with dysfunctions of the thyroid, the pituitary bodies and other organs of internal secretion.

... It seems probable that, since a chronic pancreatitis is probably a cause of dysinsulinism, the glands secreting trypsin, amylase and steapsin are often involved with either increased or decreased function."

It is on the basis of this ground breaking and comprehensive paper, one of the classics in medicine, that a motion for the adoption of the term "Harris' Syndrome" is entertained.

Harris' original paper has been followed by publications in ever increasing numbers. Contributions came from neuro-psychiatrists, internists, endocrinologists, diabetes specialists, gastroenterologists, pathologists, physiologists and surgeons. It looked as if the eyes had been opened to the existence of an entity that previously had been completely overlooked or treated as neurosis, neurasthenia, vasomotoric imbalance, vagotony, etc.

It must have been a great satisfaction to Harris when he wrote in 1936 (2) "Hyperinsulinism takes another syndrome from the waste basket of neuroses' is the syllogistic statement of Evans and McDonough of La

Cross, Wisconsin, who found and relieved six cases in six months' private practice after they became 'hyperinsulinism conscious'. Powell, a general practitioner of West Monroe, Louisiana, found 25 cases of hyperinsulinism in 2 years after he recognized his first case."

On another occasion, in closing a discussion of a paper he had read before a gastroenterological meeting, Harris made the following remark (3). "I predict that within the next year most of those present will have had one case, or a number of cases, of hyperinsulinism. In other words, when gastroenterologists become hyperinsulinism conscious, they find the cases; because such patients usually connect their symptoms with their stomachs."

This writer became "hyperinsulinism conscious" six years ago. In these six years I have seen in my private practice twenty-eight cases. From 1941 until 1943 twelve cases were seen, but no case incidence figure can be given as the total number of new patients could not be determined due to a change in the filing system. In the year 1944 I saw eight cases. As the total number of new patients seen by me in 1944 was 260, the incidence of spontaneous hyperinsulinism in my private practice in 1944 was 3 per cent. In 1945 the incidence was 1 per cent, in 1946 1.7 per cent. The incidence over the years 1944-46 was 1.9 per cent.

Among the 28 cases there were 21 males and 7 females. The age ranged between 26 and 48 years; 16 were between 30 and 39 years.

The duration of symptoms was from 3 months to 20 years, the average being $4\frac{1}{2}$ years. The appearance of the symptoms was as a rule between $1\frac{1}{2}$ and 5 hours after a meal. The symptoms occasionally started, or were exaggerated, on physical exertion. This was particularly pronounced in the case of a 38-year-old mailman, letter carrier, who for 20 years had spells while on his route. Often the spell appeared at bed-time or during the night sleep.

The symptomatology has so often been given that it may be unnecessary to repeat it here. The most common symptoms were abdominal pain, weakness, numbness, cold perspiration, tremor, dizziness, absentmindedness, lack of alertness. There were people who in a spell passed red traffic signals and were surprised when they were stopped by the policeman. There were teachers who suddenly in the classroom did not know "what they were talking about." A 32-year-old engineer performed motions that seemed strange to himself like slamming doors, missing the chain of a light switch, trying to open a door without turning the handle. When he was reading, "his eyes were far ahead of his brain."

An indefinite sensation of hunger was present in most patients during the attacks. At times, but by no means generally, there was craving for sweets. Eating, particularly ice cream and fruit juices, invariably stopped the attack.

Five patients, or 18 per cent, had diarrhea during or right after the attack.

Twenty-five patients or 89 per cent had abdominal pain. The pain was described in nearly every imaginable way from an indefinite "hunger pain" to severe cramps. The pain was localized in every part of the abdomen although the upper abdomen and the upper left abdomen prevailed.

Weight loss was recorded by eight patients, or 29 per cent. The greatest losses in weight were 35 pounds in one year, and 43 pounds in 16 months.

From patients' histories and through findings of our own the following associated pathological data seem worth reporting.

Duodenal ulcer was present in 4 patients or 14 per cent.

Achlorhydria, one patient, or 3.6 per cent.

Hyperchlorhydria, without ulcer (134 and 140 total acidity respectively), 2 patients, or 7.2 per cent.

Bradycardia (pulse rate from 52 down to 24 per minute), eight patients, or 29 per cent.

Tachycardia, one patient, or 3.6 per cent.

Emotional instability, two patients, or 7.2 per cent.

Alcoholism, two patients, or 7.2 per cent.

It was generally stated by patients that coffee aggravated the symptoms.

The glucose tolerance test was performed on twenty patients. The remaining eight patients had only fasting blood sugar determinations. The majority of these eight patients were workers in defense plants whose absence from work for a whole day did not seem justified during the war emergency. We were satisfied when the fasting blood sugars were below 65 in the presence of a typical history and when the therapeutic results bore out our diagnosis. In only one case did we extend the test to five hours as has been suggested by Harris and others, and in only four cases did we extend the test to four hours. Of the remaining fifteen cases only twelve required the three hour test whereas three showed the typical blood sugar drop already two hours after glucose intake. Of the twelve patients who had a three hour test three showed the three hour blood sugar equal to, or higher than, the two hour blood sugar. Of the four patients who had a four hour test two showed a rise of the four hour blood sugar over the three hour specimen.

It is admitted that, in shortening the test period, we may have deprived ourselves of more impressive figures of blood sugar drop. Case 13 showed the most spectacular drop of the whole series only after four hours which we would have missed had we stopped at the three hour test which already had been convincingly low. However, as all our tests were done on ambulatory patients, we could ill afford to extend them beyond the appearance of a clinical insulin shock which at times had rather alarming features. In following Harris' suggestion, we made our patients take brisk walks for about 25 minutes prior to the two, three, and four hour tests.

One hundred grams of chemically pure Dextrose Anhydrous Merck in 300 cc of water were given the patients to drink immediately after the fasting specimens were taken.

TABLE I.

Chart of Blood Sugar Tolerance Tests.

Case No.	Fasting	45 min.	2 hours	3 hours	4 hours	5 hours
1.	88	149	122	67	53	
2.	59	113	29			
3.	65	140	100	30		
4.	88	147	115	50	70	
5.	75	70	70	55		
6.	85	120	55	40		
7.	71	107	47			
8.	50	115	63	55		
9.	80	108	63	40		
10.	59	95	69	72		
11.	65	110	41	60		
12.	71	74	82	12		
13.	70	144	80	40	15	
14.	55	74	45	50		
15.	64	124	57	18		
16.	79	125	70	49		
17.	85	118	83		85	53
18.	74	156	110	38	55	
19.	75	100	79	36		
20.	70	158	29			

From our series we selected three blood sugar curves for graphic demonstration.

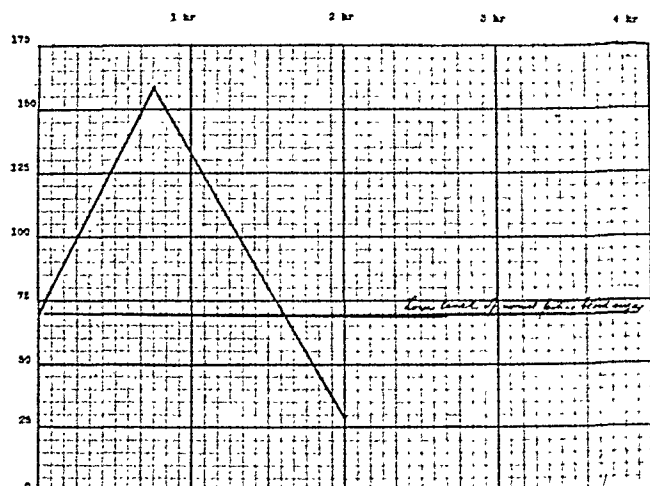


Figure 2 shows normal rise and early fall (after 2 hours)

Case No. 5 failed to show any rise of his blood sugar over the fasting value. This phenomenon is considered by Bockus(4) as indicating malnutrition. It is debatable whether this case belongs to our series at all, and the question arose whether this patients' hypoglycemia had an origin other than hyperinsulinism. However as a typical attack was produced after three hours, the case was included.

It will be noted that cases No. 13 and 15 had blood sugar drops below 20 mg per cent. These patients were not in a shock anywhere near as severe as others whose blood sugar remained much higher. This observation has been made by other writers. Sippe and Bostock(5) gave their opinion as follows. "As in all disease, the susceptibility of the individual varies so that one person

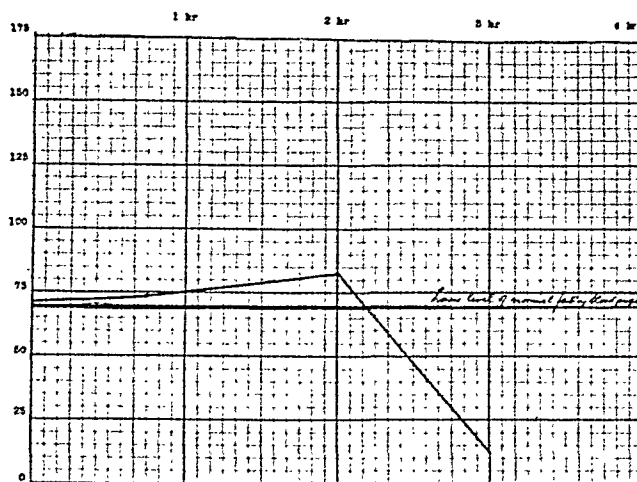


Figure 3 shows "flat" rise and average fall (after 3 hours)

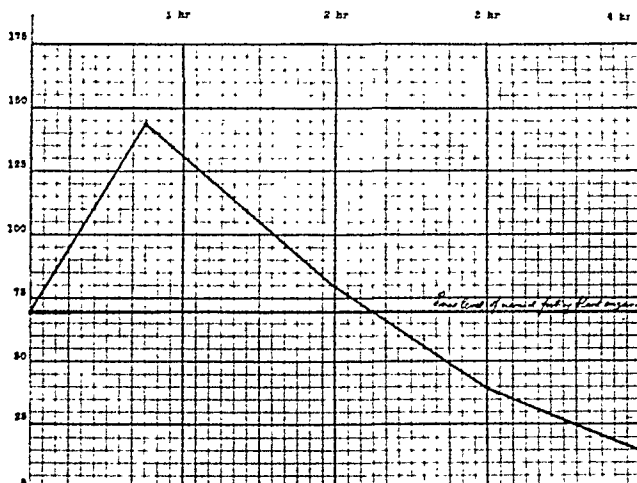


Figure 4 shows normal rise and late fall (after 4 hours).

may feel well with a blood sugar which gives rise to acute hypoglycemic symptoms in another." Banting(15) stated that hypoglycemia may not be noticed until the blood sugar falls to 32 mg per cent. Cammidge(10) made similar observations. Pribram(11) observed hypoglycemia at a blood sugar level of 80-90 mg per cent. Leyton(12) and Langdon Brown(14) reported on two diabetics who displayed symptoms of hypoglycemia at levels of 250 and 150 mg per cent respectively.

In our series, cases 2, 3, 4, 7, 11, 12, and 20 showed the most definite signs of insulin shock, the severest being case 20. It occurred to us that in all these patients the blood sugar fall was deeper and more sudden than in the rest of this survey. Within one hour the fall was in case 3: 70; case 4: 65; case 7: 60; case 11: 69; case 12: 70; whereas in case 2 the fall was 84, and in case 20, it was 129. Our observation seems to favor the opinion that a sudden marked fall of the blood sugar, no matter between what levels, is the cause of the symptoms described as insulin shock. If this opinion were confirmed by other observers, the term "Hypoglycemia" would not be adequate to characterize Harris' Syndrome. "Hyperinsulinism" would seem to cover the subject in a better way. The question of the "sudden and marked

drop" of the blood sugar has been discussed many times in the past. Maddock and Trimble(6) observed a blood sugar drop from 230 to 43 mg per cent in three hours without symptoms. Priesel and Wagner(7) made the same observation on a patient whose blood sugar dropped from 321 to 94 in four hours. Siegman(8), in an excellent and comprehensive study uttered the opinion that the duration of the existence of hypoglycemia is more liable to produce symptoms than the speed and the extent of the fall.

Siegman's opinion was not borne out by our observations. Seven patients on whom the sugar tolerance tests were performed and all eight patients who had only fasting blood sugar determinations appeared for the test in a state of hypoglycemia (65 mg per cent and below). It seems safe to assume that their hypoglycemia had existed for many hours prior to the test. Yet no one revealed any symptoms or signs of insulin shock. The cases of Maddock and Trimble and of Priesel and Wagner do not necessarily disprove our opinion that a sudden marked drop of the blood sugar will produce symptoms. The falls from 230 to 43 mg per cent and from 321 to 94 mg per cent, spectacular as they may seem, were observed over periods of three and four hours respectively. This means an average fall of 62 and 57 mg per cent per hour respectively, which is not as deep a fall as some of our patients displayed.

Another observation may seem worthy of consideration. As all of our patients were away on brisk walks for 25 minutes prior to the collection of each blood specimen, there is reason to believe that the elapse of one hour between two blood sugar determinations was too long and gave misleading results. The actual drop, or at least the major part of it, may have taken place in a much shorter time, during the walk. This observation seems to have been confirmed by Levine, Gordon and Derrick(9). These investigators determined the blood sugar of runners in a Marathon race who were stricken by sudden collapse. They found hypoglycemia as low as 40 mg per cent.

In reviewing the literature, including text books on diabetes and insulin treatment, it occurred to us that the definition of hypoglycemia differed almost with every author. Himwich(16) made the following statement. "We recognize hypoglycemia clinically only when the blood sugar has fallen so low that signs and symptoms become conspicuous. It takes a blood sugar below 50 mg per cent before such symptoms become prominent." Banting(15) set the critical level at 32 mg per cent. Pribram(11) observed symptoms at a level of 80-90, Leighton(12) at 250, Langdon Brown (14) at 150 mg per cent.

None of our patients underwent pancreas surgery. In deciding on a conservative treatment we followed the suggestions of Bockus and of Whipple and Frantz. In an attempt to differentiate between functional hyperinsulinism and adenoma of the islets of Langerhans, Bockus(4) gave eight criteria which are suggestive of

benign neoplasm. None of these criteria were applicable to any one of our patients. Whipple and Frantz(13) summarize their opinion as follows. "After the diagnosis of chronic hypoglycemia is established, — the patient should have a course of medical therapy. — If it is found — that the seizures are controlled only on a high carbohydrate intake, an exploratory celiotomy is indicated." As far as is known, all our patients responded promptly to low carbohydrate dietary treatment. None of them had any further seizure as long as the diet was observed. Except for six patients who moved away in the course of the years, a close follow-up was carried out.

Of further interest seems the following observation. This writer limits his practice to gastroenterology. It will be noted from the above mentioned data that in our series twenty-five patients or 89 per cent offered a history of abdominal pain. The pain appeared several hours after meals and was relieved by eating. It would seem only natural that physicians who are not familiar with, nor conscious of, Harris' Syndrome, may suspect in those patients duodenal ulcer. In fact twenty-one patients or 75 per cent had been under medical care, some for many years. A great many had gastrointestinal X-ray examinations, some up to three and four GI series, in search for an ulcer which did not exist. Eighteen patients or 64 per cent were referred to us for opinion by their physicians after unsuccessful treatment. It seems safe to assume that the bulk of patients with Harris' Syndrome appear in the office or clinic of the gastroenterologists at some time during their clinical course, either on their own accord or referred by their physicians "because", as Harris remarked, "such patients usually connect their symptoms with their stomachs."

The frequent occurrence of abdominal pain in patients displaying Harris' Syndrome will be easily understood if one considers the effect of insulin on gastrointestinal peristalsis. In 1924 Bulatao and Carlson(17) reported that production of hypoglycemia in experimental animals by the subcutaneous injection of insulin was uniformly accompanied by hypertonus and hypermotility of the stomach. The gastric tonicity and motility increase as the hypoglycemia deepens until complete tetanus of the stomach is reached. The first record of the increase in gastric peristalsis in the human individual after insulin administration was that by Dickson and Wilson in 1924(18).

This observation was followed by a report from Quigley, Johnson and Solomon(20) who observed that the increased peristalsis produced by insulin is not inhibited by such procedures as smoking, unpleasant emotion, body discomfort, or the presence of moderate amounts of non-carbohydrate food in the stomach. The increased movement was inhibited by Atropine. The immediate relief of the excess peristalsis and of hunger when appropriate amounts of glucose were given was observed both by Dickson and Wilson and by Quigley, Johnson and Solomon.

According to Best and Taylor(19) insulin augments

also, to some extent, peristaltic movement in the duodenum and in the colon, but the effect is not as marked as in the case of the stomach. However, increased peristalsis in the colon may account for the fact that five patients or 18 per cent of our series had diarrhea during or right after the attack.

Since those early observations on the effect of insulin on gastric peristalsis it has become known that insulin also raises gastric secretion and acidity. The close interrelationship between fall of blood sugar and rise of acidity was amply demonstrated by Hollander in a recent publication(21).

The established stimulating effect of insulin on gastric peristalsis and on gastric secretion may be a temptation for speculating on the subject of "hyperinsulinism and peptic ulcer." Abrahamson devoted much thought and wrote an interesting article on this subject(22). He found a gradual drop of the blood sugar level from the peak reached after glucose intake to an average of 58 mg per cent in the six hour specimens in twelve patients with proven gastric or duodenal ulcer and in four patients with negative X-ray findings but with "ulcer histories". However, none of his cases displayed the recognized symptoms of hyperinsulinism, and therefore his terminology differs from the generally accepted one. Moreover in nearly all cases his blood sugar drops were slow and continuous to levels that in themselves are not low enough to make up for the absence of symptoms.

In our sugar tolerance tests we ran across many cases that failed to show any symptoms. Those cases were not included in this series although we obtained blood sugar values as low as 60 and even 56. We felt that if a person goes long enough without eating, anyone may produce a low blood sugar level. That is probably the normal mechanism for producing hunger. We all will get "weak from hunger" if we stay long enough without food, and six hours is a pretty long stretch if a man had just seven tablespoonsful of sugar for breakfast.

In our series four patients or 14 per cent had proven duodenal ulcer, none had gastric ulcer. This incidence seems to be too low to draw any conclusions. On the contrary, it may be argued that gastric hyperperistalsis and hyperacidity are not, or not alone, the cause of peptic ulcer.

A great number of other diseases have been suggested as having some causative relation to hyperinsulinism. However, as the majority of these reports were made after only one case had been observed they don't seem to carry too much weight. Those associated diseases were "hypophyseal thinness", primary carcinoma of the liver, trichinosis, rhabdomyofibroma, retroperitoneal sarcoma, alcohol intoxication, "hypophyseal disease", hypophysectomy, perforated duodenal ulcer with secondary pancreatitis, renal glycosuria, "smoke drinking", Raynaud's Disease, Simmond's Disease, trigeminal neuralgia. Hypoglycemia was even called "a new deficiency syndrome in Spain."

Of our series the only associated abnormality worth noting seems to be bradycardia, observed in eight patients or in 29 per cent. These bradycardias, with pulse rates ranging from 54 down to 24 heart beats per minute, were observed during routine physical examinations, not during the sugar tolerance tests.

Abdominal pain, as reported above, was present in 25 cases or in 89 per cent of the series. The high incidence of this symptom makes us hesitate to call abdominal pain an associated abnormality in Harris' Syndrome. It seems much rather to be almost an integral part of the clinical picture.

Weight loss was reported by eight patients or 29 per cent of the series. This weight loss was marked in two cases, 35 pounds in one year, and 43 pounds in sixteen months. As in both these patients the symptoms as well as the blood sugar drops were very marked, they were presented to one of New York's leading pancreas surgeons. In both cases surgery was refused, and patients did well and regained their weights under dietary management.

The ratio between males and females, if our survey of twenty-eight cases carries any weight in this respect, is somewhat different from reports in the literature. Cammidge(10) found that every age period, excepting 31-40, showed an excess of males, about two to one. Sippe and Bostock(5) had 21 females as against 4 males. Our series consisted of 21 males as against 7 females. Of these seven females one was 26 years old, three were between 30 and 40, and three were between 40 and 50 years old.

Where the overall case incidence is concerned, the only reference found in the literature was made by Sippe and Bostock(5). These authors found a case incidence of 0.47 per cent whereas ours was 1.9 per cent. This discrepancy may be explained by the difference in material. Sippe and Bostock drew their cases "from a large series of cases met with in general medical practice" whereas ours was a selected group in a comparatively small gastroenterological practice, the majority of the patients having been referred by their physicians because of undiagnosed digestive disturbances.

SUMMARY AND COMMENT

A suggestion was made to introduce the term 'Harris' Syndrome' for spontaneous hyperinsulinism in honor of Doctor Seale Harris who first described this clinical entity in 1924.

Twenty-eight cases of Harris' Syndrome were seen by us in private practice between 1941 and the end of 1946. The overall case incidence was 1.9 per cent. This figure indicates a higher frequency of occurrence than is hitherto generally believed. A great many more physicians should become "hyperinsulinism conscious" in order to avoid diagnostic pitfalls, as for example this writer has not one case of hyperinsulinism registered in his files prior to 1940, although he has been in medical practice for 24 years.

The most common and cardinal symptoms of Harris' Syndrome in our series were abdominal pain, weakness, cold perspiration, tremor, dizziness, impaired consciousness. No attempt was made in this paper to touch the psychiatric angle of this disease. However, it should be mentioned that an extensive psychiatric literature exists on this subject. This literature includes reports on inmates of state institutions who had been treated as epileptics till the true nature of their "fits" was found. We may add here the history of one of our patients who once, while sitting in a movie theater, became unconscious and wetted himself.

On 20 of our 28 patients glucose tolerance tests were performed, the remaining 8 cases having been diagnosed if the fasting blood sugar was below 65 mg per cent and if the therapeutic results were satisfactory. It was found that the typical blood sugar fall occurred much earlier than is generally believed. The average deep fall occurred after 3 hours. There were early falls after 2 hours. A fall after 4 hours was found to be a late

fall. A 5 hour determination was necessary in only one case. Blood sugar falls below 20 mg per cent were seen on patients on whom no subsequent surgery was seen to be indicated. In fact none of our patients were subjected to surgery although blood sugar falls were usually down to lower levels than hitherto seems to have been the rule in case reports on non-surgical hyperinsulinism. The extent and the speed of the blood sugar fall were found to be the important factors in the causation of symptoms.

The frequency of abdominal pain in our patients' histories was noted which makes this symptom almost an integral part of Harris' Syndrome. This pain seems to be due to the known effect of insulin on gastric and intestinal peristalsis and on gastric secretion and acidity. It is therefore suggested that gastroenterologists be particularly alert to the relative frequency of Harris' Syndrome in patients presenting "ulcer histories" on whom no diagnosis of ulcer can be made. No causative relationship between hyperinsulinism and peptic ulcer was found.

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An Explanation of Anal Pruritus*

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NONE OF THE published explanations of anal pruritus that have come to my attention have been convincing. It therefore seems worth presenting a simple and seemingly logical explanation based upon a personal experience with this annoying disorder. My experience was practically an experience of experimental anal pruritus as the itching developed under unusual experimental dietary conditions and alternately subsided and recurred with changes in my diet. The circumstances were as follows:

In 1914, I began swallowing large amounts of cotton fiber as a non-nutritive substitute for food to make food restriction or fasting easier. The fiber (surgical cotton

cut up or chopped up so as to reduce its tendency to mat) was hard to swallow without suitable flavoring and I found no entirely satisfactory non-nutritive flavor. Hence, I generally swallowed the fiber after soaking it in orange juice or some other fruit juice. This, without other food, served to satisfy me during periods of about 3 days after which more nourishing food seemed to be needed and was eaten during 1 or 2 days. Then I would again return to the exclusive use of cotton fiber soaked in fruit juice. This regimen of alternately restricting and liberalizing my food intake appeared to be highly beneficial but it became complicated by the development of intolerable anal pruritus and therefore had to be abandoned.

The diet of cotton fiber and fruit juice was obviously

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responsible for the pruritus as the anal itching disappeared intermittently with the eating of more normal food and it also did not occur when the cotton fiber was swallowed after it was soaked in olive oil or when it was taken mixed with tapioca jelly or other food. A time factor was apparently involved in the development of a sensitive anal condition as I did not notice any itching until a month or more after I began using large amounts of the cotton fiber soaked in fruit juice. First, it was noted that itching followed the anal leakage of small amounts of fluid. Later, paroxysmal itching (as if an insect were biting) occurred after the apparent mere passage of small amounts of gas. However, with the passage of gas, the simultaneous anal leakage of fluid was noted on a few occasions. Drying the anal region did not stop the itching under these circumstances. Washing the region was necessary to bring relief. This suggests that even without noticeable anal leakage, anal pruritus may be produced by an insensible leakage or insensible spraying of the anal region with irritating fluid carried along by passing gas.

In the above experience, the fruit juice did not seem to be carried into the rectum. The feces appeared to consist of practically nothing but cotton fiber in the form of discrete boluses. When only lemon juice was used as flavoring, the cotton passed about as white as when it was taken, excepting for periodic bile staining. The discrete fecal boluses of cotton nevertheless contained enough fluid so that small amounts were evidently separated from time to time by periodic peristaltic waves or by the transiently increased pressure created by the movement of gas. Unlike normal food fiber, cotton fiber holds fluid loosely and releases it easily under pressure. Normal cellulosic food residues usually include hydrated cellulose and hemicellulose from which fluid cannot easily be separated by simple pressure.

It does not seem likely that unabsorbed fruit juice was the fluid responsible for the anal irritation. Gastric juice also does not seem to be the fluid likely to explain irritation below the duodenum. This leaves bile, pancreatic and intestinal juices as the most probable sources

of the irritating fluid, at least in my experience. In other cases, irritating or decomposing foods may be responsible. However, in my opinion, tryptic corrosion is mainly responsible for anal pruritus and also for the scalding effect of diarrhetic stools, lower bowel soreness following diarrhea and the initiation of lower bowel ulceration. The infection of lower bowel lesions is secondary, according to this concept.

The circumstances under which I developed anal pruritus may nevertheless lead some psychosomatic minded clinicians to question the foregoing explanations on the assumption that my practice of swallowing cotton fiber and the restriction of my food intake had no rational basis and indicated an abnormal psychologic condition which was somatically manifested by anal pruritus. In fact, my sanity was questioned in some medical quarters because of my use of cotton fiber and other non-nutritive materials but the idea was appreciated by Dr. Frederick M. Allen when it was brought to his attention in 1917. Before that, Dr. Allen had demonstrated the value of the starvation treatment of diabetes at the Hospital of the Rockefeller Institute for Medical Research and he realized that a flour made of something like cotton fiber would help make the starvation treatment of diabetes more practical. As a result of Dr. Allen's encouragement, I placed a cellulose flour (Cellu Flour) on the market in 1919 and this became widely used in the dietary treatment of diabetes before insulin was discovered. After insulin became available (in 1923), I disposed of my manufacturing interests in Cellu Flour, partly because insulin was then expected to make food restriction or fasting unnecessary in the management of diabetes and the value of food restriction or fasting for other purposes was not (and still is not) widely appreciated. In recent years, increasing evidence has nevertheless been found by tests on rats that food restriction (1) and intermittent fasting (2) prolongs the life span. In fact, the mere addition of cellulosic bulk-formers to the diet of rats has also been found to prolong the life span (3, 4). My use of cotton fiber and periodic food restriction or fasting therefore seems to have been amply justified.

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Pruritus Ani

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PRU^RITUS ANI is a syndrome, the most distressing feature of which is itching. It is because of the intense suffering it causes, the nerve racking agony, chronicity, unyielding to treatment, and frequent recurrence, that it is so prominent a problem to the profession. This condition resulting from numerous diseases, local or constitutional, taxes the skill and ingenuity of the physician, brought forth legions of treatments; medical, surgical, X-ray, physiotherapy, chemotherapy, prophylaxis, vaccination and hydrotherapy. It is still an urgent and provocative subject — discussed and interrogated among proctologists — “How do you treat Pruritus Ani?” They eagerly listen and absorb voraciously all helpful suggestions. Many brilliant physicians throw up their hands in despair when encountering these afflicted patients, and wish they could avoid such cases. This symptom looms up as a giant in the sphere of therapeutics, grim, tenacious and elusive. Symptomatic treatment consumes the energies of most of the profession, whether admitted or not — and here is a symptom that has driven some to nervous exhaustion, despair, and even suicide!

ETIOLOGY

The causes of pruritus ani are very numerous, usually a combination of many conditions. It may follow as a sequence of many diseases, as diarrhea, constipation, nervous and physical strain, particularly if there is pre-existing ano-rectal disease. The itching at first may be very mild, transient, but if scratching is started the tissues are injured, inviting infection. At first the person may feel a sense of relief after rubbing and scratching, but later the itching becomes worse, and the urge to scratch very intense; so, a vicious circle is started — undermining all nerve control, establishing the scratch-itch syndrome. If this scratching continues the perianal tissues become altered, diseased and the condition goes from bad to worse.

One fact must be emphasized and I found it undeniably true, that itching can be precipitated in many cases, if scratching is persistent even if the person is in the best of health, in general, and without any ano-rectal disease in particular. Persistent abuse by anything that is harsh to the tissues would invariably produce itching. Because this region is perpetually in contact with enormously bacteria-laden masses, nature erected a line of defense in these tissues against infection. If mechanical force as scratching, rubbing, irritation by clothing, chemicals, etc., the barriers are destroyed and infection results. Once the tissues are denuded, the sensory nerves are exposed and itching begins. The

abundance of nerve supply in this region, renders it very susceptible to irritation, resulting in itching, burning, smarting, pain and spasm especially when they are exposed.

Pruritus may follow ano-rectal diseases, colon and sigmoid-cryptitis, fissure, fistula, proctitis, ulcer, papillitis, prolapse, dysentery and constipation — Dermatologic diseases of the parts or adjacent tissues; eczema marginatum, dermatitis venenata, scabies, intertrigo, herpes, psoriasis and especially the most frequent tinea trichophytina. Reflex: stone in bladder, phimosis, vesiculitis, diseases of the uterus and adnexa, displacement or procidentia, ovarian cysts and tumors, and vaginal discharges. Constitutional diseases; diabetes, malaria, acidosis, T. B., Lues-anemias. Dietary — overeating, excessive carbohydrates, spiced foods, cheese, nuts — foods causing allergic reactions as sea foods. Drugs: quinine, cocaine, cinchophen, arsenic, copaiba — also strawberries in season, too much of tobacco and alcohol. Infection, bacterial, parasitic, pediculi, threadworm, tape worm, round worm, and streptococcus fecalis. Irritation from tight clothing, detergents, moisture, abrasions, skin tags, rough toilet paper, newspaper, uncleanness, sweating especially in stout individuals. Psychic conditions — melancholy, hysteria. Occupations — working in high temperature as fire engineers, stokers, moulders.

As indicated the causes of pruritus are numerous. Still, there are many cases, where there is no definite etiology found, after the most careful investigation. Here possibly the intestinal bacterial flora is the causative agent. Here the perianal tissue appears healthy, soft, good color, but the itching, and stinging are very intense. Such cases are usually due to a perineuritis of the anal canal.

Pathology: The area affected may be localized — patchy, but usually is circumanal. The tissues of the anus may be reddened, swollen, dry or moist. The radiating folds are turgid. The appearance of the skin in all cases is leathery, thick, fibrosed and hardened. There may be raw areas and fissures. The entire skin may look like a dry fig. In some cases the skin of the scrotum, perineum, is involved. It may also extend to the abdomen, thighs, knees and legs. At times, rashes and eczematous conditions affect the entire body, buttocks, labiae, penis, lumbar regions, and upper extremities. There also may be maceration, and oozing. The glands of the groin may be enlarged. Goldbacher claims that there are microscopic lacunae (lakes) in the subcutaneous tissues in pruritus. The sweat glands of the region produce a high carbohydrate, protein, and alkaline sweat, favoring the growth of bacteria and fungus.

There may be moderate discomfort in the anal region, a slight occasional itch, a transitory mild episode, during the day, or night, or after defecation while using tissues. Gradually, if scratching is done, the itching becomes severe, sharp, stinging, burning, intense and torturing. Occurring as it does at night, in most instances, it destroys the restful hours of sleep. The itching may be paroxysmal, with periods of remissions, or constant with varying intensity. In chronic conditions the tissues become tender, swollen and produce actual pain and heaviness. At night the mind is fixed to the condition and scratching is attempted, and so undermines the nervous stability. The itching at times shifts from the perianal tissues into the anal canal, perineum, scrotum and penis, vulva, groins and gluteal regions.

Treatment

The treatment of pruritus ani is to treat the causative factor, which should be searched for with the utmost diligence. At times, however, as mentioned before, the search is futile. The treatment, like the etiology, is very extensive, varied, and no treatment is a sure cure. There is no specific treatment. A combination of many methods is usually helpful. Removal of ano-rectal pathology should be carefully attempted, as fissure, ulcer, fistulae, enlarged papillae, diseased crypts, and proctitis. Even then, the itching may not cease, and sometimes becomes worse.

A conservative approach frequently brings very good results. Cleanliness is of the utmost importance, as washing the anus and adjacent tissues with a mild soap and warm water, using cotton, not rubbing, but sponging gently after defecation. Tight and irritating clothing should be removed. Rest in bed when there is inflammation and much itching is present, in a position where the anal folds are separated. Hot water sitz baths, hot towels carefully applied, or the ice bag is agreeable to some. A fan blowing directly on the inflamed areas. Hot sitz baths with potassium permanganate used at intervals is helpful. Hot low enemas are beneficial.

Mild local applications should be considered first, in the form of ointments, powders, and lotions containing carbolic acid, calomel, benzocain, chlorotone, menthol, etc. Dusting powder of various combinations containing benzocain, starch, zinc oxide, etc. Dermatologic conditions, eczema, herpes, trichophyton, erythema, sulphur, salicylic acid, Balsam of Peru, pure ichthyol, should be incorporated in the ointments. Inflamed hair follicles with pustules should be opened, drained and dusted with sulphathiazole crystals. If the skin is moist, carbolated calamine lotion with cocain should be painted at intervals. Pediculosis should be treated with Larkspur lotion. Threadworm infestation, lime water enemas daily 6 oz to each sitting; calcium sulphid gr $\frac{1}{2}$ TID, santonin Gr 2, three successive nights followed by saline purgative, infusion guassia 5%. In tinea, trichophyton, the feet should be examined and treated, also the fingernails. Saturated solutions of potassium permanganate painted on twice daily is helpful. Fissures and excoriations an

application 80% phenol and neutralized with tincture benzoin, or silver nitrate stick application, neutralized with tincture of iodine. Elimination of vaginal and rectal discharges, also pelvic and cervical pathology should be removed. Autogenous vaccines—from the isolated streptococcus fecalis, streptococcus viridans, or streptococcus hemolyticus sometimes may help. The use of trichophyton vaccine is of doubtful value. Staogen an ointment, claimed to liberate nascent oxygen has been suggested to be of value. Other drugs used, carbol-fuchsin, Whitefield ointment, citrine ointment, 5%, scarlet red ointment in vaseline.

Constipation, if present, should be treated with laxatives as cascara, milk magnesia, vegetable preparations as Siblin, or Regulon. In elderly persons, or where there is rectal stasis a glycerin suppository should be inserted. Diarrhea should be checked according to the cause.

The nervous element must be considered, as it is so often present in pruritus ani. Sedation—phenobarbital, bromides, carefully administered. Rest, fresh air, sea bathing, fresh water bathing, avoidance of fatigue and nervous irritability, combat insomnia, are measures of importance.

Diet should consist of abundance of green vegetables, kale, peas, string beans, carrots, spinach, cauliflower, milk, cereal, and fruits. Moderate amounts of fresh meat, fowl, baked fish, are allowed. Foods like oysters, lobster, clams, cheese, pickles, sausage, smoked and pickled meats, salted fish are to be avoided. All foods that are allergy provoking, like strawberries, should not be used. Avoidance of alcohol, oversmoking, and over-eating is imperative. Exclusion of such drugs as quinine, cinchophen, arsenicals, belladonna, opium, and cocain.

X-rays give good results, especially in cases where the skin is dry, not macerated or inflamed, or trichophyton infection. It should be applied three consecutive times, at weekly intervals, then a rest of several months. Plain vaseline should be applied after each treatment. Ultra-violet rays, Kromyer lamp rays are of some aid occasionally.

Injection treatment is intended to produce a circum-anal anesthesia which relieves the itching temporarily and at times permanently. The anal region where the irritation is located should be injected, after the spot where the needle enters is injected with 2% novocain. The most useful are the oil-soluble anesthetics: Neothel—(Cassa & Co., N. Y.). Benocol (Yoemans & Gorch) & Anucain. These should be slowly and evenly injected, starting at the posterior commissure, 20 to 30 cc., guarding the needle with a gloved finger in the rectum, first injecting one side and then the other without withdrawing the needle. Or the anal region can be divided in four quadrants and each injected subcutaneously, at one time, or separately. These injections of anesthetic oils can be repeated if necessary. The Goldbacher method of injecting 5% phenol in flaxseed oil in the tissues, and under the mucous lining of the rectum does not produce

any results of note. The needle he recommends is clumsy and the oil if not injected properly produces a slough. Quinine—Urea Hydrochloride, $\frac{1}{2}\%$ —30 to 60 c. c.—injected slowly until the pruritic area becomes elevated is helpful. This can also be repeated—(Hirschmann). Hydrochloric Acid 15 to 20 c. c., 1-3000 injected well under the skin along the anal canal, and the perirectal spaces, after injecting the skin with novocain, followed by massage for several days. This treatment may give desired results, but often causes abscess formation and sloughing. Alcohol injection destroys the nerve endings supplying the tissues. Here caudol, general anesthesia, or pentathol should be employed, injecting 95%, or absolute alcohol, 10 cc. mixed with 10 cc. saline, slowly, distributing carefully on both sides of the involved perianal tissues, not too near the sphincters, nor too superficial intradermally. Sloughing of the skin results frequently. This is an effective procedure, requiring hospitalization, and should be followed by hot sitz baths for several days.

Oxygen injection into the subcutaneous tissues is done in the same manner as other injections. The needle can be inserted at the lateral borders or at the posterior commissure, after it is attached to slip on piece, connected to the rubber tubing of a gas tank. The oxygen is turned on, allowing a slow flow, until the tissues are well bulging, guiding the distention by hand pressure, to prevent a widespread extension to other areas, as scrotum, vulva and lower abdomen. Many patients complain of dizziness, faintness and headache following this measure, but it is never serious. This may be repeated, and is of fair value as a therapeutic agent.

Tattooing with mercuric sulphide can be executed under local caudal or pentathol anesthesia. The skin is carefully prepared and a thick mixture of red mercuric sulphide is smeared on heavily. Also, the tattooing needle is immersed in the mixture, very often during the process, and the tattooing done evenly, diligently, driving the pigment into the tissues, which should be stretched, to open the folds and crevices. A better technique to follow, is to remove all skin tags, external hemorrhoids, hypertrophied skin folds, to produce a smooth and even surface for the tattooing. The needle is held between the index and middle fingers, at 45 degree angle, carefully tattooing the entire surface, one inch beyond the anal-margins. This renders the tissues red for a long time, or permanently. Good results are usually obtained.

Surgery—should be applied only after other attempts have failed to bring a cure. It should be as the last resort, the purpose of all surgical procedure is to cut the sensory nerves supplying the pruritic area. Also all ano-rectal pathology should be eliminated before attempting surgery, as fissure, tags, fistula, cryptitis, erosions, hypertrophied skin folds. This should be done at one time, or better at several sittings.

In those cases where there is a fissure, neuralgic pain in the anal canal, spasm, burning sensation in the anus,

divulsion should be done, under a local, caudal or pentathol anesthesia, followed by packing for drainage.

The removal of a circular, ring-like section of the pruritic tissue, and suturing the edges (Manheim) has been done, with only fair success. At times the sutures break, and where the anal rim is pruritic, the operation will be a failure. The removal of the offending tissues, and transplanting with healthy skin flaps from the surrounding areas has the same objection. Tattooing, followed by a neurotomy done with a special needle, with blunt edges, undermining the entire region is a good procedure and may give good results.

Balls operation, can be done under local, caudal, or general anesthesia. There are a few modifications of this procedure, but the principle is identical, giving the same results. As mentioned, the object is to divide all the sensory nerve filaments supplying the anal skin, the anal canal and circumanal region, which spring from the 3d, 4th, sacral nerves. An incision is made on each lateral side of the anus, excluding the perineal and coccygeal raphes, and carried by blunt dissection, raising the flaps toward the anus as far as the external sphincters. The skin flaps are put back into position and suturing the edges with interrupted cat gut sutures. This should be done thoroughly and extend under the skin to the transitional membranes of the anus. Rubber drains or vaseline gauze are inserted under the undermined skin for 48 hours. A small tube is also inserted into the rectum. Krauses modification of the Ball operation, consists of making several radiating incisions from the anus toward the normal skin, each section is undercut, and a long strip of vaseline gauze is pulled through and later cut in sections and removed. This operation gives satisfactory results, in cases of long duration, where other methods have failed.

In the author's series of 418, men were slightly more affected than women 1.2-1; Age 85% between 25-55; children 10% between 3-5 years having pin worms; 5%—5-15 years, married women with children 5-1 single; smokers 10-3 non-smokers. Alcoholics 3-1; nervous persons, and other mental defects 80-5; sedentary occupations 4-1; those who handle strong chemicals and gasoline 10-2.

Constitutional diseases—diabetes 10% yielded to treatment easily; gout and rheumatism 5%, liver disease 10%, lues with condylomata 2%, pernicious anemia 2%, allergy 1%, definite ano-rectal pathology including dermatological conditions 45%, constipation 12% diarrhea 2%, unknown or indefinite pathology 11%.

Results of treatment from the above series cannot be definitely stated, because of many recurrences, lack of accurate follow-up observations, and because of some patients terminating treatment abruptly. Also, because the greatest majority of patients received more than one treatment. However, a rough estimate can be formulated: 10% yielded to conservative regimen, as ointments, cleanliness; sitz baths, diet, powders, rest, sedation, avoidance of scratching, and light treatment.

X-ray 5%; injections of oil soluble anesthetics 3%; quinine urea hydrochloride 3.5; alcohol injection 15%; tattooing 15%, tattooing and neurotomy 20%; oxygen injection 1.5%, vaccine 1%; Ball operation 24%, divulsion 3%. There were recurrences in almost all therapeutic measures and none were 100%. As a final word in the discussion of results, the term of improvement would possibly be more applicable. Indeed, the improvement in the itching syndrome is the criterion, and the mentioned percentages would appear more real and logical in the light of such an assumption.

Comment—The etiology of pruritus ani is numerous, and so is the treatment. Because of its severity, and great difficulty in therapeutics, it is almost considered as separate entity. One method of combating it may or may not produce relief, but a combination of methods succeeds better. It can be produced by mere persistent scratching especially where there is a nervous element present. Successful treatment, first and foremost depends upon stopping the scratching. Very careful investigation should be carried out, both local and general conditions, before any intelligent treatment is under-

taken. Cleanliness should be rigidly insisted upon. The patient should be told that he must cooperate, and that this symptom is hard to cure, in a brief period. As to the method of treatment, cleanliness is extremely important. Injections of anesthetic oils, quinine, urea hydrochloride, are usually of temporary value.

Oxygen treatment is of doubtful importance. Hydrochloric acid injections in my series were not useful. Tattooing resulted in a few cases, with cures. Tattooing and neurotomy were still better than tattooing alone. Alcohol injections were very useful—producing many cures, but a few recurrences were present. Ball operation, which should be the last resort, resulted in the most cures, with an extremely small percentage of recurrences.

Here is a condition that calls forth skill, patience and fine judgment, of the physician when facing such a distressing problem. From the many suggestions and cures mentioned, like a huge store of good material, the physician should be able to select excellent means for effective and successful treatment.

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An Evaluation of the Antacid Activity of Protein Hydrolysate Using Graduated Doses in the Human Stomach

By

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THE NUTRITIONAL value of amino acid mixtures (protein hydrolysate) in hypoproteinemia is established (1) (2) (3). The amphoteric character of protein hydrolysate enables it to have an antacid effect on gastric acidity (4) (5). The often associated gastric hyperacidity and hypoproteinemia of chronic peptic ulcer patients suggested to Co Tui and his associates that protein hydrolysate might be used in the treatment of that disease. Their reports (3) relative to symptomatic relief were phenomenal and the antacid effect seemed gratifying.

It is not within the province of this presentation to discuss the symptomatic relief of protein hydrolysate M.R.T.* That phase will be discussed in a later article at the completion of a current study. Since Co Tui and his co-workers reported (3) in part on the antacid effect of protein hydrolysate in doses of 25 and 50 grams, this author became interested in studying the duration of antacid effects of graduated doses of protein hydrolysate.

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METHOD

Fully cognizant that extrinsic and intrinsic factors do influence the gastric acid secretion (6) (7) (8) (9), every effort was made to standardize the conditions under which the patients were studied. The fifty-six patients used in this study were ambulatory cases with gastrointestinal symptoms but not necessarily with gastroduodenal disease.

Two studies were conducted on each patient. They reported at 9 A. M. on each of the two occasions without having ingested anything, not even water, for at least nine hours. The first study was carried out one hour after the ingestion of six unsalted Uneda Biscuits and twelve ounces of tap water. The second study was carried out every fifteen minutes for ninety minutes after the ingestion of a protein hydrolysate—M.R.T., white Karo syrup and water mixture.

The fifty-six patients were divided in eight equal groups. The dose of protein hydrolysate varied for each division. Every patient of the first group of seven received fifteen grams and this was increased by five grams for each patient of the succeeding groups. Therefore, each of the last group of patients received fifty grams of protein hydrolysate. In every instance

Modified Ewald
Gastric Analysis

Schedule 1 — Fifteen Grams P-H Used

Case No	F. A.	1 hour T. A	15 min.		30 min.		45 min.		60 min.		75 min.		90 min.		Remarks
			F.A.	T.A.	F.A.	T.A.	F.A.	T.A.	F.A.	T.A.	F.A.	T.A.	F.A.	T.A.	
1	50	84	0	130	0	116	56	100	68	126	74	110	78	120	TW
2	20	40	0	200	30	200	40	130	60	96	64	100	58	86	TW
3	0	10	0	124	0	140	0	130	60	100	40	82	55	90	TW
4	36	80	0	156	0	150	20	146	74	122	90	130	94	118	TW
5	48	90	36	108	50	162	86	128	56	76	48	70	10	30	NTW
6	10	24	0	104	0	102	0	100	0	96	50	72	52	96	TW
7	48	74	0	200	44	114	78	100	108	236	140	220	152	260	TW

Schedule 2 — Twenty Grams P-H Used

Case No	F. A.	T. A	15 min.		30 min.		45 min.		60 min.		75 min.		90 min.		Remarks
			F.A.	T.A.	F.A.	T.A.	F.A.	T.A.	F.A.	T.A.	F.A.	T.A.	F.A.	T.A.	
8	40	65	0	100	28	58	48	80	30	50	46	60	50	65	TW
9	10	30	0	200	0	240	0	196	0	188	40	110	95	155	TW
10	28	44	0	126	0	110	35	70	40	80	38	60	50	65	TW
11	20	48	0	220	0	200	0	196	50	120	70	148	60	84	TW
12	36	60	0	230	0	170	0	168	0	132	0	120	45	100	NTW
13	12	42	0	256	0	174	0	146	0	200	60	120	56	142	NTW
14	12	38	0	225	0	216	0	200	0	156	40	132	62	126	TW

Schedule 3 — Twenty-five Grams P-H Used

Case No	F. A.	T. A	15 min.		30 min.		45 min.		60 min.		75 min.		90 min.		Remarks
			F.A.	T.A.	F.A.	T.A.	F.A.	T.A.	F.A.	T.A.	F.A.	T.A.	F.A.	T.A.	
15	50	38	0	160	0	260	0	220	50	150	50	120	45	110	TW
16	25	40	0	240	0	160	0	150	0	126	0	108	0	94	TW
17	35	64	0	264	0	248	0	244	0	242	0	210	10	182	TW
18	30	58	0	236	0	200	0	188	0	164	0	152	0	146	TW
19	30	55	0	260	0	240	0	228	0	184	40	160	48	132	TW
20	38	60	0	160	20	45	36	124	54	96	46	90	40	64	TW
21	38	56	0	240	0	254	60	148	74	136	80	144	96	162	TW

Schedule 4 — Thirty Grams P-H Used

Case No	F. A.	T. A	15 min.		30 min.		45 min.		60 min.		75 min.		90 min.		Remarks
			F.A.	T.A.	F.A.	T.A.	F.A.	T.A.	F.A.	T.A.	F.A.	T.A.	F.A.	T.A.	
22	36	50	0	240	0	226	0	188	0	168	54	146	86	104	TW
23	40	64	0	260	0	248	0	220	0	180	40	130	36	112	NTW
24	35	55	0	160	0	210	0	240	0	224	0	210	0	164	NTW
25	20	40	0	240	0	210	0	184	0	168	0	150	40	148	NTW
26	55	80	0	278	0	262	0	244	0	230	80	140	68	122	NTW
27	35	48	0	210	0	192	0	180	0	164	24	110	42	96	NTW
28	38	60	0	180	0	164	0	150	0	140	60	110	40	106	TW

Schedule 5 — Thirty-five Grams P-H Used

Case No	F. A.	T. A	15 min.		30 min.		45 min.		60 min.		75 min.		90 min.		Remarks
			F.A.	T.A.	F.A.	T.A.	F.A.	T.A.	F.A.	T.A.	F.A.	T.A.	F.A.	T.A.	
29	0	14	0	280	0	264	0	250	18	178	36	160	50	142	TW
30	40	68	0	264	0	236	0	200	0	186	14	162	28	114	TW
31	44	80	0	220	0	246	0	238	0	216	0	194	0	168	TW
32	20	35	0	186	0	174	0	162	0	150	26	108	40	98	TW
33	50	74	0	114	0	160	0	154	0	132	12	120	16	114	TW
34	40	68	0	232	0	246	0	220	14	202	28	184	44	160	TW
35	30	64	0	210	0	188	0	176	0	168	30	152	44	138	NTW

Schedule 6 — Forty Grams P-H Used

Case No	F. A.	T. A	15 min.		30 min.		45 min.		60 min.		75 min.		90 min.		Remarks
			F.A.	T.A.	F.A.	T.A.	F.A.	T.A.	F.A.	T.A.	F.A.	T.A.	F.A.	T.A.	
36	18	34	0	276	0	238	0	214	0	196	0	164	0	142	NTW
37	58	82	0	286	96	210	98	188	106	218	94	222	86	114	TW
38	40	60	0	280	0	268	0	254	0	240	90	150	70	148	TW
39	44	72	0	220	0	198	0	190	0	184	0	168	0	154	TW
40	50	74	0	280	0	252	0	228	48	172	88	164	102	160	TW
41	52	80	0	266	0	240	0	210	0	180	93	156	60	96	NTW
42	38	50	0	182	0	174	0	150	12	132	30	142	32	168	TW

Schedule 7 — Forty-five Grams P-H Used

Case No	F. A.	T. A	15 min.		30 min.		45 min.		60 min.		75 min.		90 min.		Remarks
			F.A.	T.A.	F.A.	T.A.	F.A.	T.A.	F.A.	T.A.	F.A.	T.A.	F.A.	T.A.	
43	14	20	0	280	0	256	0	230	0	182	0	160	30	124	TW
44	12	26	0	244	0	228	0	212	0	178	40	162	56	138	TW
45	16	34	0	290	0	278	0	256	0	218	0	184	44	126	TW
46	30	55	0	296	0	280	0	264	0	250	0	230	18	178	TW
47	18	34	0	240	0	228	0	208	0	188	0	172	32	164	TW
48	28	44	0	298	0	274	0	262	0	236	28	194	54	136	TW
49	12	26	0	288	0	262	0	244	0	228	20	186	46	154	TW

Schedule 8 — Fifty Grams P-H Used

Case No	F. A.	T. A	15 min.		30 min.		45 min.		60 min.		75 min.		90 min.		Remarks
			F.A.	T.A.	F.A.	T.A.	F.A.	T.A.	F.A.	T.A.	F.A.	T.A.	F.A.	T.A.	
50	40	64	0	278	0	278	0	284	0	260	0	224	0	192	TW
51	45	62	0	294	0	276	0	254	0	254	0	218	24	176	NTW
52	70	95	0	226	0	214	0	188	0	156	0	142	28	108	NTW
53	28	50	0	280	0	248	0	248	26	200	30	184	42	150	NTW
54	46	84	0	286	0	254	0	228	24	212	46	200	76	182	TW
55	35	53	0	310	0	326	0	294	0	290	0	264	0	240	TW
56	10	20	0	242	0	198	0	182	0	164	18	136	28	122	TW

Key:

P-H — Protein Hydrolysate-(M.R.T.)

F.A. — Free HCl

T.A. — Total Acidity

TW — Tolerated well

NTW — Not tolerated well

the medicament was mixed with two tablespoonsful of white Karo syrup and dissolved in six ounces of tap water. Gastric extraction was conducted by way of a Levine tube and rubber bulb glass syringe. The extracted specimens were filtered through four layers of gauze. An analysis for free hydrochloric acid and total acidity was carried out in the usual manner using Topfer's reagent and also phenolphthalein as indicators and N/10 sodium hydroxide for titration.

CONCLUSIONS

Schedules 1 to 8 present the acid figures obtained in each of the studies. The following was deducted from these schedules:

(1) Tolerance to protein hydrolysate—M.R.T. seems to depend more on the individual's reaction rather than to the amount ingested, if the maximum amount does not exceed fifty grams. All of the patients in Schedules 3 and 7 tolerated the medicament well. Only two of Schedule 4 tolerated the protein hydrolysate well. Four to six patients from each of the remaining groups also were able to tolerate the drug.

(2) In most instances, after taking the protein hydrolysate mixture, as the free HCl returned and increased the total acidity decreased.

(3) At the end of one hour:

(a) Of the fifty-six patients studied twelve had higher free HCl figures after the ingestion of the protein hydrolysate than after the modified Ewald meal; one had the same and six patients had lower free HCl figures. Thirty-seven patients gave no reaction for free HCl.

(b) Since the total acidity at this time is higher than after the modified Ewald meal, some of the amino acid mixture must still be present. The free HCl figures of the twelve cases mentioned above tends to suggest that when the protein hydrolysate ceases to have an antacid effect it might even act as a stimulator for gastric acid secretion. This suspicion seems to be confirmed in the figures obtained at the seventy-five and ninety minute studies.

(c) The antacid effect of protein hydrolysate begins to decrease at this time. Therefore, either another dose of this medicament must be given or a supplementary

antacid should be used at the end of one hour in peptic ulcer patients.

(d) Six patients of Schedule 1 had a return of free HCl. The remaining seven groups had three or less patients with returned free HCl at the one hour period. However, it did not necessarily follow that the larger the dose of protein hydrolysate used, the lower would be the number of cases in which the free HCl returned. For example: The patients of Schedules 4 and 7 did not have a return of free HCl but some of the patients of Schedules 5, 6 and 8 had free HCl at the end of one hour.

(4) Regardless of the size of the dose (up to fifty grams) of protein-hydrolysate, at the ninety minute period five or more patients of each group had a return of free HCl. Thirty-eight of the fifty-six cases studied had higher free HCl figures at the ninety minute period after the ingestion of the protein hydrolysate mixture than at the one hour period after the modified Ewald meal. Since the total acidity figures at the ninety minute period revealed evidence that amino acids were still in the stomach, one tends to conclude that the protein hydrolysate is, at least in part, responsible for the rise in the free HCl at that time. It seems that as the protein hydrolysate ceases its antacid activity, it reverses itself and acts as a stimulator for the formation of Free HCl.

SUMMARY

This study was conducted to determine the length of time that graduated doses of protein hydrolysate would be antacid in effect when ingested. With doses increasing up to fifty grams, it seems that the best antacid effect is at one hour. The "thirty" and "forty-five grams" groups got the best results.

While protein hydrolysate has an antacid effect, it nevertheless had best be supplemented with another antacid at the end of one hour. There is apparently a tendency for it to become a stimulator for the secretion of free HCl in the stomach at the end of one hour or at least when its antacid activity has been spent.

²This is to express appreciation to Marvin R. Thompson, Inc., Stamford, Conn., whose grant of Protein Hydrolysate—(M.R.T.) made this study possible.

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Addition of Casein to Mixed Protein Diet.

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DURING the recent past the use of a special dietary nitrogen source as a means of increasing nitrogen intake has become increasingly popular in medical practice. (e.g.,6). Such preparations have, hitherto, been evaluated experimentally by studies in which they have been offered to laboratory animals as effectively sole source of dietary nitrogen (e.g.,3). Data obtained on such a basis, while of substantial value, unfortunately provide little information as to the effect of such a preparation on a given diet. Equally, it is true that data obtained with any one diet can hardly be extrapolated to apply to other diets. Nevertheless a diet can be chosen to represent an estimated average American dietary protein intake such as that given by Block (2) and data obtained on the effects of adding some special dietary nitrogen source to such a diet are not without interest.

In this communication some results obtained by adding casein to such a dietary mixture are presented.

EXPERIMENTAL

The composition of the protein mixture was made up to simulate that given by Block (2). Table I shows this mixture.

A protein mixture containing the components in the last column of Table I in proportions determined by the nitrogen content of each and the percentages in column 3 was made up and thoroughly mixed by tumbling. It assayed 9.35% N, equivalent to 58.5%

TABLE I

Makeup of Basal Mixed Protein Ration
Estimated Average
per Capita Consumption

Protein Source	Pounds protein % total protein	Protein chosen as representative
Dairy Products	14.9	20.8
Meats and Fish	27.3	38.2
Eggs	5.7	8.0
Beans and Nuts	4.0	5.6
Cereals	19.6	27.4
Total	71.5	100.

protein, and will hereafter be referred to as Basal Mixed protein.

Rations were prepared in accordance with the schedule given in Table II. These rations were freshly prepared at ten day intervals and were stored in a refrigerator except when actually handled.

Groups of seven animals each were taken by random selection from a shipment of Sherman strain

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*It is a pleasure to acknowledge the stimulation of several conversations with Dr. George R. Cowgill concerning these experiments.

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TABLE II

Ration	Composition* of Rations Fed					% N in finished ration
	Basal Mixed protein	Casein (GBI)	Cornstarch	VMFR	Water	
A	100gm.		610 gm.	140gm.	150ml.	1.05
B	100	12.5gm.	597.5	140	150	1.17
C	100	25	585	140	150	1.33
D	100	50	560	140	150	1.68

*This composition of experimental rations is similar to that currently used in rat repletion studies at the University of Chicago (Cannon, P. R., private communication). The mixture represented by the symbol VMFR is a combination of vitamins, minerals, fat and roughage whose composition is Ruffex, 500 gm.; Lard, 400 gm.; Osborne and Mendel salt mixture, 400 gm.; Liver extract concentrate 1:20 (Armour), 100 gm.; Oleum percomorphum, 30 drops; calcium pantothenate, 127 mg.; pyridoxine hydrochloride, 60 mg.; riboflavin, 83 mg.; choline chloride, 18 gm.; thiamin hydrochloride, 54 mg.; niacin, 134 mg.

weanling male rats (23-25 days old; average weight 40-60 gm.) received from Rockland Farms. All animals were caged individually in mesh bottom cages. Each animal had free access to water, from individual bottles refilled daily. Weighed quantities of rations were offered six times weekly (double portions on the day previous to the day to be skipped) and food consumption records kept for each animal. The rations were offered in china dishes held in "scatter proof" sheet metal containers. Ration quantities offered were sufficient to make the feedings *ad libitum*.

The animals were weighed at five day intervals. At the end of 30 days the experiment was terminated. (One animal in group B died on the third day of the experiment. Autopsy revealed a defective gut so this death was ignored in evaluating the results.) An average protein efficiency ratio was calculated for each group by dividing the weight gain of each animal by the total equivalent of protein ($N \times 6.25$) consumed and averaging these individual ratios within groups.

Table III summarizes the experimental data and the calculated protein efficiencies.

DISCUSSION

In evaluating these results it must be borne in mind that these are not true supplementation studies in the

TABLE III
Results of Thirty Day Rat Growth Tests.

Ration	No. of Rats	Average		Food Intake gm.	Protein Efficiency*
		Initial Wt. gm.	Final Wt. gm.		
A	7	53.7	120.3	441	2.30 \pm 0.17
B	6	52.7	133.9	470	2.36 \pm 0.34
C	7	54.0	150.0	494	2.30 \pm 0.12
D	7	52.4	130.3	432	1.69 \pm 0.39

*Limits given correspond to the 95% confidence interval, calculated by the methods of the A.S.T.M.(1).

sense that the effects of mixtures of proteins fed at the same level are compared with the results of feeding the individual proteins at that level, such as, for example, the experiments of Sabine and Schmidt (4). Rather do these experiments reflect the consequences of simultaneous change of protein concentration in the diet and modification of the amino acid pattern offered to the animal, in the same manner as Sure's experiments (5). Because of this, interpretation of results is not easy. However, such a technic tends to simulate many dietary conditions under which protein supplements are employed practically; somewhat more closely, perhaps, than evaluations based on the use of such materials as the sole source of dietary nitrogen.

In any case the protein efficiencies shown in Table III indicate that there is little or no change in the rat's ability to use the mixed basal protein for growth when the protein content of the ration is increased from 6.3% (Ration A) to 8.3% (Ration C) by addition of casein. However raising the protein content to 10.5% (Ration D) by another increment of casein shows a highly significant decrease in protein efficiency. Since casein alone at the 10% protein level has usually been found, under similar conditions of test to have a protein efficiency of about 2.2 (unpublished observations) this is difficult to explain. However similar ef-

fects have been noted in other experiments and it may well be that this situation is a reflection of cases where protein efficiency is maximal at low levels of intake and decreases rather sharply.

Perhaps the simulation would be further improved if the supplement were not offered incorporated in a test ration. Experiments to explore this technic are contemplated. In any case the experimental approach outlined here must not be regarded as a substitute for classical technics of protein evaluation. Nitrogenous foodstuffs (either proteins, protein hydrolysates or amino acid mixtures) used for supplementary purposes should be of high biological adequacy *per se*; then it becomes worthwhile to examine their value as dietary accessories.

The potential ramifications of such a technic are literally enormous but intelligent choice of basal protein mixtures and incremental levels should lead to the accumulation of much interesting data.

SUMMARY.

An experimental design is described which reproduces, to a first approximation, the conditions under which dietary protein supplements are used in practice.

Some experimental results, using casein as auxiliary dietary nitrogen source, are given.

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Editorial

TOTAL PANCREATECTOMY

WHOEVER IS IN CHARGE of arranging a program for a medical meeting, especially for a staff meeting of a hospital, will read with the greatest interest the proceedings from a conference at the Mayo Clinic on "Total Pancreatectomy". This was a meeting which sets an example for other such conferences, and many of us will study its coordination and high level of discussion. The surgeons, the head of the department of experimental medicine, the medical department, and the laboratory staff, all joined in presenting their sides of this topic. By this arrangement, a complete survey of this very difficult and highly interesting field was achieved, with special attention to the metabolism after this heroic operation. We feel sorry that we have to be satisfied with reading these proceedings instead of having been able to attend this conference.

Total pancreatectomy was first performed by Rockey in 1943. His patient survived only 15 days. This should be compared with the first case from the Mayo Clinic. There, a survival time of 37 months was reported.

The conference was based on four cases observed at the Mayo Clinic. The first patient had an islet cell tumor. For several years he had suffered from severe fainting spells with a drop of blood sugar to 30 mg. After total pancreatectomy, he was able to resume his normal activities. The insulin requirements were 18-26 units a day. The number of stools varied with the intake of fat.

The second case was also that of an islet cell tumor. The patient's spells were accompanied by a blood sugar drop to 24 mg; however, they were never accompanied by unconsciousness. The removal of the entire pancreas was done in two stages. After operation, the insulin requirements were the same as in the first case.

In the third case, the patient had a diabetes mellitus. A carcinoma of the pancreas was found. The blood sugar was 130 mg. before the operation, while the patient was taking 20 units of protamine-zinc insulin daily. After operation, the diet contained 272 gr. of carbohydrate, and the diabetes was well controlled by 10 units of protamine-zinc and 30 units of regular insulin daily.

The fourth case was that of a chronic pancreatitis

with diffuse calcification of the pancreas. Total splenectomy, total pancreatectomy, resection of the lower part of the common duct, partial gastrectomy, and partial duodenectomy was performed. The patient stood this tremendous operation well and returned home. She had the same insulin dosage as the previous case. She died following a severe insulin reaction which was not recognized. In this connection, Bollman mentioned the fact that the main cause of death in depancreatized animals was overtreatment with insulin. He called attention to the fact that fatty livers may develop after this operation.

Sprague discussed the observations on the diabetes that followed total pancreatectomy. Following the removal of the pancreas, the diabetic state was quickly established. It was interesting that the insulin requirement of the reported cases was less than that of many cases of severe diabetes. It is especially important to watch for prolonged hypoglycemic reactions, and therefore insulin has to be used with considerable caution. In case 3, the insulin reaction was only slightly more severe after operation than before operation. This increased requirement of insulin probably was due to a greater intake of carbohydrates and protein, and the lower intake of fat than in the diet customarily used. The effect of total pancreatectomy on the capacity of the liver for manufacturing sugar may be important.

Comfort reported on digestion and absorption in these cases. The weight of fecal solids was from two to three

times the average weight of stools of normal persons. Fat composed about 40-50% of the fecal solids. That is much greater than similar values in normal persons, which is approximately 8% fat contents of their stools. The protein contents was also higher than normal and derived from undigested and unabsorbed protein. Most of this loss of fat may be attributed to the loss of external secretion of the pancreas. Digestion and absorption of carbohydrates appeared to be remarkably good. The concentration of plasma lipoids in the blood stayed within normal range. The post-operative diet was a problem because of the difficulty in gaining weight and because of abdominal distress and frequent bowel movements. Concentrated pancreatin in the form of coated tablets had to be administered, 15 gm. daily. The caloric contents of the food had to be increased 40% above normal. A high protein, high carbohydrate diet, with fats in amounts tolerated, was found to be most suitable.

This clinical meeting and the later published report on this condition, was of the greatest interest, not only for the advancement of surgery, which permitted the removal of the entire pancreas with good results, but also because of the studies in metabolism of the pancreas. More and more frequently we are able to diagnose islet cell tumors instead of calling our patients neurotic.

FRANZ J. LUST

Total pancreatectomy: a symposium. Proceedings of the Staff Meeting of the Mayo Clinic. 21, 2, 25. Jan. 23, 1946.

Obituary

DOCTOR ISIDORE WILLIAM HELD was born in Austria, May 15, 1876. He received his Doctorate of Medicine from Jefferson Medical College, Philadelphia, in 1902. He continued post-graduate work in Berlin and Vienna, for four and one-half years (1907-08; 1910-11; 1913-14; 1921-22; 1926-27), under such internationally prominent men as Professors Edmund von Neusser, Hans Eppinger, Herman Strauss, Friedrich Kraus, Ludwig Pick, Adolph Bickel and Theodore Brugsch.

Doctor Held was connected with the Beth Israel Hospital in New York City for the past forty years. He had served as attending physician and later as consulting physician. He was also consulting physician in numerous hospitals both in and about New York City. He was clinical professor of medicine at the New York University College of Medicine from 1935 to 1941. He was an inactive major in the United States Medical Reserve Corps.

Doctor Held's training and preparation was broad in scope for internal medicine. This is evident by the time spent during his visits to Berlin and Vienna in studying various subjects. He studied hematology under the direction of Professor Pappenheim, chemistry, especially uric acid studies, in the laboratory of Professor Friedrich Kraus, experimental gastro-intestinal studies in the laboratory of Professor Adolph Bickel. Doctor Held was always interested in clinical pathology, never having missed a session of interest where such topics were discussed.

Doctor Held was the author of 86 original monographs and articles dealing with gastro-enterology, hematology, roentgenology, cardiology and medical biography. He is co-author with Dr. M. H. Gross of a translation from the German of "Differential Diagnosis of Internal Medicine" by Matthes (1925). Also, together with Dr. M. H. Gross, of a translation from the German of Wegele's work entitled, "Therapeutics of the Gastro-Intestinal Tract" (1913). In 1946 his medical work entitled, "Peptic Ulcer — Its Diagnosis and Treatment" was published, which was co-authored with Doctor A. Allen Goldbloom — who has been his associate for over twenty years.

Doctor Held has been Diplomate of the American Board of Internal Medicine since 1937; Fellow of the American College of Physicians since 1931; Fellow, New York Academy of Medicine; Fellow, American Medical Association; Fellow, National Gastro-enterological Association since 1934; member of the American Heart Association, the American Association of the History of Medicine, the American Association for the Advancement of Science, the New York State and New York County Medical Societies, Association of Military Surgeons, American-Soviet Medical Society and several other local medical societies.

In 1941 money was raised by his friends for the establishment of the "I. W. Held Fellowship Fund" at the New York University College of Medicine.

His greatest field of endeavor was that of gastro-

intestinal diseases. Held was the first to state that the niche of a peptic ulcer is essentially a diverticulum; if not adherent to an adjacent organ it is a pulsion diverticulum, but if there is traction on the niche, as a result of perigastritis, it is both a pulsion and traction diverticulum.

In 1912 he was one of the first to call attention to the fact that in coronary sclerosis with coronary spasm (even without coronary thrombosis) there may be abdominal symptoms of such a nature as to simulate an intra-abdominal disease such as perforated gastric ulcer.

Held was one of the internists who was a believer in clinical entity of chronic (recurrent) appendicitis. Held stated that in retro-cecal appendicitis, the pain, although persistent in the right groin, is referred to the appendicular region if pressure is exerted over the right groin — Held's sign of appendicitis.

In his recent monograph on "Peptic Ulcer — Its Diagnosis and Treatment", Held was in the opinion that of all the various theories of the cause of peptic ulcer,

the one most acceptable is that of the constitutional factor. This theory explained the finding so often observed in individuals where there is a high stomach and low colon or a low stomach with a high colon.

Held had modified the treatment of intractable peptic ulcer by advocating the introduction of the duodenal tube into the jejunum. This is known as jejunal feeding. This method has proven to be more satisfactory than the others because it is better tolerated by the patient. The tube is introduced away from the site of the ulcer and prevents nausea.

Doctor Held's early studies in hematology had aroused his interest in the clinical pathological consideration of lymphadenopathy. He considered the conception of dividing the lymph node into two structural components, the corticomedullary portion and the reticulo-endothelium portion. The main function of the former is to produce lymphocytes while that of the latter was similar to the reticulo-endothelial system elsewhere in the body.

A. ALLEN GOLDBLOOM.

NOTE

Professor Leo L. Hardt, of the Loyola University School of Medicine, recently stated at a meeting of the American College of Physicians, that a palatable mixture of *mucin* and *aluminum magnesium trisilicate*, by forming a rather durable coating for the inside wall of the

stomach, was yielding unusually rapid healing of even deep peptic ulcers, most of which filled in within a period of five or six weeks, even without the dietary precautions usually employed in ulcer cases. The long distance results of this treatment will be watched with interest.

Book Review

TOMORROW'S FOOD. By James Rorty and N. Philip Norman, M. D., pp. 258, (\$3.50), Prentice-Hall, Inc., New York 11, N. Y., 1947.

This is a good and sound book which takes a broad view of nutrition and assembles facts from far and wide and ends up with valid conclusions. I appreciate the authors' references to the "healthy Hunzas", because I was taken to task some eight years ago for filling a page of this Journal by a review of a book dealing with the supernormal health of the Hunza nation (Jan. 1939, Vol. V, No. 12, p. 755). This book "The Wheel of Health: a study of a very healthy people" was written by G. T. Wrench, M. D. and published by C. W. Daniel, London, England. The diet eaten by the Hunza nation resulted in a superlative degree of health such as has never before been encountered in the history of man. There was practically no illness and old men retained the characteristics of youth. McCarrison's animal experiments proved that the diet partaken of by the Hunzas was the cause of their remarkable health. The present authors re-iterate the main points of Wrench's book, namely, that the value of the diet depended upon intensive horticulture, unusually efficient soil fertilization and seed development. I still feel that the Hunza experience with food constitutes the most challenging fact in the history of human health, that it deserves intensive re-study by American dietetic scientists and points to the next really big movement in diet perfection, — special-

ized soil fertilization and "tagged products". It seems almost certain that food products cultivated under these special conditions will be found to contain essential elements beyond the recognized accessory food factors, familiar to us today.

The present authors emphasize the dangers inherent in regulating diets by subtractions, and state that the American diet suffered from these deprivations for many years, and that, even today, we have distorted patterns of food production, processing and distribution. Bread justifiably receives much criticism, especially manufacturing processes which remove natural vitamins and then artificially resubstitute them by "enriching". Rudolph Steiner's ideas are referred to, for what they are worth. Biodynamic farming obviously is something for the distant future. England leads America in the use of compost heaps, due partly to the pioneering work of Howard. The problems of food processing, canning, distribution and labeling are dealt with in an interesting way. The book is an enlightened plea for national health through eating. The final chapter "How to eat sensibly without vitamin charts" comes like a refreshing cold towel to the forehead of one who, jammed between scientific erudition and the petulance of a brow-beaten, vitamin-conscious public, sometimes longs to trade medical practice for the quieter, though equally disputatious, avocation of horticulture. Here is a book not to miss.

Beaumont S. Cornell.

Abstracts of Current Literature

(Microfilm copies of papers may be obtained from the Microfilm Service of the Army Medical Library at 25c per each complete article, not exceeding 25 pages in length—and 10c for each additional 10 pages or fraction thereof. Prepayment is not requested. Remittances may be made with subsequent orders and in such manner as found most convenient. Address—Microfilm Service, Army Medical Library, Washington, D. C.)

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CLINICAL MEDICINE

MOUTH AND ESOPHAGUS

LEDERER, J. AND RENAER, M.: *Le syndrome de Plummer-Vinson et son traitement par la thérapeutique martiale parentérale.* (*Acta Gastro-Enterologica Belgica*. Feb. 1947, X, No. 2, 71-73.)

The authors detail 3 cases of Plummer-Vinson syndrome in which marked clinical improvement occurred following the parenteral administration of iron. The dysphagia was relieved within 10 days and the glossitis even more quickly. The cacodylate of iron was used. The authors believe that the elevation of the level of the blood serum iron is the main point in the remarkable improvement, rather than the elevation of the red blood cell count and the hemoglobin percentage, and that the serum iron acts as a biocatalytic agent on the enzymes of the bodily cells involved.

STOMACH

WEIG, CLAYTON G.: *Benign ulceration within a duodenal diverticulum.* (*Radiology* 48,2,143. Feb. 1947.)

Diverticulosis of the duodenum is seen frequently enough that the lesion can no longer be called uncommon. On the other hand, benign primary ulceration of the small bowel, except in a Meckel's diverticulum, is still a rarity. The combination of the two lesions, namely a benign primary ulcer within a duodenal diverticulum is a rare pathology. Although the reported case has not been proved from the pathologist's point of view, it exhibits the usual radiographic signs of benign ulceration as seen elsewhere in the gastrointestinal tract, both in the acute phase and in the interval stages to complete healing.

During fluoroscopy in erect position, in spite of visualizing the entire sweep of the duodenum, the pathology could not be seen, however, films taken in prone position demonstrated the lesion. The main complaints of the patient were epigastric pains.

BROHEE, GEORGES: *Stase duodenale reactionelle.* (*Acta Gastro-Enterologica Belgica*. Feb. 1947, X, No. 2, pp. 74-85.)

Brohee, in an article well illustrated by X-ray film reproductions makes out a good case for the reality of reactionary duodenal stasis. Functional stasis (to be

distinguished from organic stasis due to adhesions) may at times be normal, or at other times represent an abnormal physiology. In the latter case, Brohee names it "reactionary" by which term he implies that definite trouble exists in one or several functions of the organ, humoral or toxic in nature. Among the factors inducing hypo- or hyperperistalsis in the duodenum, he includes the dysequilibrium resulting from the antagonistic actions of the ortho- and parasympathetics, acetylcholine, adrenalin, and the ions, calcium, potassium magnesium and sodium. The reactionary stasis may involve all or only a portion of the duodenum and may be of reflex origin. Duodenitis may be a factor. Diagnosis depends on careful serial radiograms. The duodenum, capable of causing intractable nausea, should be carefully examined in hepatitis, cholecystitis, peptic ulcer and appendicitis.

LAUBSCHER, J. H. AND SMITH, A. M.: *Pyloric Stenosis in Twins.* (*Am. Journ. Dis. Children*. March, 1947, 73, 3, 334-341).

Literature, reviewed by the authors, show 53 sets of twins each suffering from pyloric stenosis. "When pyloric stenosis affects uniovular twins, both infants show the condition and when pyloric stenosis affects the binovular twins, the disease is likely to occur only in one twin" (Sheldon). A few exceptions (4) have been found to both parts of this rule. The authors present binovular twins both having pyloric stenosis. Both were admitted to hospital within 3 days of each other about a month after birth because of projectile vomiting. Operation in each twin revealed a typical hypertrophied pylorus, and both were cured. A study of the literature does not lead to any definite conclusions concerning possible genetic factors in the etiology. A twin is not more likely to be affected than an infant who is not a twin.

BOWEL

FISHBACK, H. R., JR.: *Carcinoma of the transverse colon in a fifteen-year-old boy.* (*Radiology* 48,2,168. Feb. 1947.)

According to the author, this is the 38th case of carcinoma of the colon reported in children of fifteen years or younger. The history of this case is very interesting. This white boy was admitted to the hos-

pital in March 1945, the chief complaint being "stomach cramps" of three weeks duration. He had previously had a number of similar attacks of abdominal cramps, the first occurring in 1943, two years before admission, at which time the pains lasted about one to two minutes over a period of 24 hours. There had been no nausea, vomiting, diarrhea, constipation, bloody or tarry stools, associated with the pains. Beginning in August 1944, the cramps became more frequent and more severe until the middle of February 1945, when the pain was intense and the patient vomited about once every twenty-four hours. During the three weeks prior to admission to the hospital, he had lost 15 pounds in weight. Bright red blood was seen once in the stools. An abdominal mass could not be felt. The roentgenological examination revealed a typical, complete obstruction in the middle of the transverse colon. The pathological diagnosis was that of an advanced adenocarcinoma of the signet-ring type, undergoing colloid degeneration.

EUPHRAT, ERWIN J.: *Roentgen features of mucocoele of the appendix.* (Radiology 48,2,113. Feb. 1947.)

- A mucocoele of the appendix varies in size from a slight localized enlargement of the appendix to a globular mass ten cm in diameter or more. It is usually benign but, in the event of rupture into the peritoneal cavity, pseudo-myxoma peritonei may result. Woodruff and McDonald, however, present evidence to support the belief that this malignant complication can arise only when the cyst is the seat of an adenocarcinoma, none of eight benign cysts encountered with rupture having eventuated in this fashion. But, since there are no means of distinguishing the malignant from the benign forms of the disease, except by histologic study, any diagnostic method which will increase the frequency of its pre-operative recognition is of more than academic importance.

Anatomically, there are certain features of the disease which should render it susceptible of roentgen diagnosis in many instances. When the cyst attains sufficient size, it will produce significant displacement and deformity of the cecum, to which it is attached. For the same reason, if the cecum is mobile, and it usually is, the mass will move with it. Calcific deposits in the wall or substance of the cyst are of no infrequent occurrence. The closed nature of the cyst makes its lumen impermeable to contrast media administered orally or by enema, unless patency is reestablished. The latter situation is known to occur, but only very rarely reported.

The roentgenological features of a mucocoele of the appendix are: a sharply circumscribed, globular or reniform soft-tissue mass, with considerable motility, but firmly attached to the cecum. Medial displacement of the cecum by this mass. Calcium deposits in the wall or substance of the mass, failure of the appendix to fill with contrast agent, and a vortical appearance of the folds of cecal mucosa support the diagnosis.

SAUER, LEO, M. D., Ph. D.: *Epidemic Diarrhoea of the New Born (Neonatal Enteritis).* (Illinois Med. J., Apr. 1947, 91, No. 4, 201-204.)

Epidemic diarrhea of the new born presents a prodromal period, characterized by lack of appetite, increase in the number of stools, progressive daily weight loss, and in this stage it cannot be differentiated from dietary indigestion except by the fact that infants do not respond to dietary adjustments (protein, milk, boiled breast milk) but rather develop vomiting, abdominal distention, ashen gray color, listlessness, fever, precipitous loss in weight, watery stools and toxicity. In the 1927 epidemic at The Cradle, Dr. Gladys Dick, a founder and benefactor of The Cradle made an exhaustive study of these cases in collaboration with George Dick, M. D., and J. Lisle Williams and isolated the Morgan dysentery bacillus from the minute intestinal ulcers in every fatal case only when the proper culture medium was used (in a recent British epidemic, a virus was isolated). The disease may carry a mortality as high as 32 per cent of those attacked. The best treatment is prevention. An aseptic feeding technic is described which has thus far been 100 per cent efficient in preventing spread of the disease.

RAPOPORT, S., DODD, K., CLARK, M., AND SYLLM, I.: *Postacidotic State of Infantile Diarrhea: symptoms and chemical data.* (Am. J. Diseases of Child.: April, 1947, 73, 4, 391-441.)

Following diarrhea in infants, after the stage of acidosis and dehydration, low levels of calcium, potassium, phosphorus and phosphatase are encountered. The reduction in these ions is thought to be caused by their rapid uptake by previously depleted body tissues. The post-acidotic phase of diarrhea is characterized by a clinical picture consisting of lethargy or irritability, convulsions, respiratory embarrassment, derangements of cardiac function, intracranial and gastrointestinal hemorrhages and generalized edema. Less often classic signs of peripheral tetany, carpopedal and laryngeal spasms, are seen. These clinical manifestations appear related primarily to the hypocalcemia. Correction of acidosis by alkalizing agents may accentuate the tendency to postacidotic disturbances. Calcium salts have been of benefit in preventing or curing the postacidotic phase of diarrhea. Large doses of calcium frequently are required.

SAWYER, K. C.: *Carcinoma of the Colon.* (Northwest Medicine, April 1947, 46, 4, 278-283).

The author points out that by reason of modern improvements in diagnosis and treatment, colonic cancer has become more and more curable, being today the most curable visceral malignancy. Palpation can detect 60 per cent of all colonic cancers. Before operation, rehabilitation of the patient is undertaken by improving the fluid, electrolyte, protein and vitamin balance. Whole blood transfusions in large amounts constitute the best

and most rapid single factor in this procedure. Decompression of the colon either by cecostomy or colostomy in the presence of obstruction is a pre-operative imperative. The best method of reducing the incidence of peritonitis is by giving succinylsulfathiazole. The dose used is one-fourth gram per kilogram of body weight given as an initial dose and repeated every four hours. The stool becomes odorless and scanty and gas and distention are relieved almost immediately. Cleansing enemas are used, but discontinued 48 hours before operation. He presents 6 complete case histories.

NASIO, JUAN: *Local Sulfanilaminotherapy in Chronic Thromboulcerative Colitis by Means of Single or Double Colonic Tube*. (Rev. Gastroenterology, April 1947, 14, 4, 253-258).

The author uses a tube to deliver suspensions and solutions of the sulfonamides directly to the site of lesions anywhere within the colon and has obtained X-ray and endoscopic evidence of healing. The method is used in conjunction with the usual dietary and other means of treatment.

ODDY, J. G. AND CLEGG, H. W.: *An Outbreak of Staphylococcal Food-Poisoning*. (Brit. Med. J., April 5, 1947, 442-444).

An outbreak of toxic food poisoning among miners who partook of pressed pickled beef sandwiches is described. The cause was found to be *staphylococcus pyogenes aureus* (phage type 47/47C). The infection originated in a butcher who had a throat and nasal infection as well as a minor, infected cut on the palm of his hand. All the cases occurred among miners employed on the day shift. No cases developed among the afternoon and night shifts, and it was shown that this agreed with the fact that the organism required 17 to 25 hours to produce effective amounts of toxin; the sandwiches which caused the disease having been made the previous day. Enterotoxin can be produced by this organism under a wide temperature range. The symptoms were explosive and alarming with dizziness, nausea, vomiting, diarrhea and abdominal pain. All the 167 persons affected were improved after 24 hours and normal in 3 days. Obviously meat handlers should be inspected for nasal and manual infections and strenuously treated with the sulfonamides and/or penicillin as a public health measure.

BROWN, PHILIP W.: *Inflammatory Disease of the Bowel*. (Proceedings of the Staff meetings of the Mayo Clinic, April 16, 1947, 22.8, 155-156).

In the specific group, the inflammatory diseases most commonly encountered are due to organisms of the genera *Salmonella*, *Shigella* and *Staphylococcus* and to the parasite, *Endamoeba histolytica*. Cases labelled "intestinal flu" sometimes turn out to be instances of

infection with *Shigella dysenteriae*. Sulfadiazine is regarded as the drug of choice for the treatment of bacillary dysentery. In amoebic infestations the best treatment is the prompt institution of two courses of emetine hydrochloride combined with two or three courses of an arsenical drug. The most effective arsenical is treparsol, but as it has not yet returned to the market, carbasone is employed. In the non-specific group, the two diseases most commonly encountered are chronic ulcerative colitis and regional ileitis. Important factors, from an etiological standpoint are (1) emotional and mental stress (2) food intolerance with respect to one or two dietary items, ordinarily harmless and (3) acute intercurrent infections such as the common infections of the upper respiratory tract or acute diarrhea. No drug or antibiotic agent has more than an assistive value. 'Surgery has only the same value here as a gastroenterostomy in duodenal ulcer.

WAKEFIELD, E. G.: *Medical Aspects of Malignant Lesions of the Anus, Rectum and Colon*. (Proceedings of the Staff Meetings of the Mayo Clinic, April 16, 1947, 22, 8, 153-155).

This is a succinct review largely of what the physician can do in preparing for operation a patient suffering from a malignant lesion of the colon, rectum or anus. Search for metastases should be made, but a moderately enlarged liver ought not to preclude laparotomy. Patients who suffer from such associated conditions as heart or kidney disease, diabetes, hyperthyroidism, gout or indeed any chronic disease should be studied for the purpose of evaluating the limits of function of the systems or organs involved in the associated disease process, and this sometimes must cause delay in operation, and the use of such therapeutic agents as digitalis, insulin and antibiotic agents, as well as intravenous introduction of fluids if dehydration or hyperazotemia is present. Anemia associated with cancer of the right portion of the colon usually is of the hypochromic type which responds to blood transfusions. For a few days prior to operation the patient is hospitalized and given saline laxatives (e. g. saturated solution of sodium acid phosphate, as well as colonic irrigations twice daily). Obstruction is combatted, when possible by the use of nasal suction and fluids intravenously although the latter do not replace all the electrolytes lost through nasal suction.

SURGERY

THOREK, MAX: *Surgical Aspects of Cholecystitis*. (Rev. Gastroenterology, April 1947, 14, 4, 236-239).

The author has found that electrocoagulation, or electrosurgical obliteration of the gallbladder, is better than classical cholecystectomy, because drainage is eliminated, there is no leakage, shock usually is eliminated and mortality reduced.

Prolapse of Redundant or Hypertrophied Gastric Mucosa

By

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THE INCIDENTAL finding of prolapsed gastric mucosa into the duodenum occurs frequently enough that further study is warranted to evaluate its etiology, pathology, symptomatology, and treatment. Scott in a recent article, felt that this condition is more than just a roentgenographic variant and should be considered a clinical entity. Our interest in this condition was first stimulated by witnessing several fluoroscopic demonstrations of prolapse with the comment of a radiologist and an internist, that this probably has no clinical significance; yet the patient entered the clinic with complaints simulating peptic ulcer and no other lesion could be demonstrated by the roentgen examination.

Bockus believes that only severe prolapse associated with gastritis, can cause symptoms and then, only after producing partial pyloric obstruction. He further states that gastric symptoms produced by such prolapse are so rare that they have no practical significance. In a recent personal communication, Dr. W. C. Alvarez states that the roentgenologic appearance of prolapsed gastric mucosa usually has no significance and does not explain the symptoms; his roentgenologist has practically stopped reporting the peculiarity.

Further impetus was provided by Dr. A. Melamed of Milwaukee, who demonstrated to us twenty-five cases of prolapsus with symptoms relieved either medically or by surgery. It has been Scott's experience that in the past few years, the characteristic filling defects seen in this condition are often misinterpreted and confused with duodenal ulcers, duodenitis, or similar disorders. Most of the literature on this subject is contained in x-ray journals and it is felt that the attention of the gastro-enterologist should be drawn to the importance of this subject. Therefore, a review is presented, together with 4 cases, observed in this hospital within as short a period as a few months.

In 1926, Eliason, Pendergrass, and Wright first described the roentgen signs produced by such a prolapse. Melamed found only 19 proven cases in the literature which, with his published case, made a total of 20 as late as 1943.

Archer states that prolapsing gastric mucosa is not rare, but gives no figures, and Feldman reports an incidence of redundant gastric mucosa in approximately 0.1% of all gastro-intestinal cases with the observation that the condition is not recognized until mucosa pro-

lapses into the pyloric canal.

Scott surveyed the incidence in a large naval hospital:

Total Hospital Admissions	19,228
Upper G. I. Series	1,346
Percentages of Upper G. I. series:	
Gastric Ulcer	13 (0.96%)
Duodenal Ulcer	325 (24.1%)
Duodenitis	17 (1.3%)
Prolapse	14 (1.04%)
Gastric Tumors	0

One must bear in mind that his clinical material was obtained from healthy young males on active duty in the Navy. It is interesting to note that the incidence of prolapsus slightly exceeds that of gastric ulcers. The incidence of 1.04% is higher than that reported by Rees, who found prolapses in 4 out of 3000 consecutive x-rays in one series, and 2 in 2,550 in another, which is about 0.1%, as reported by Feldman. Scott feels that prolapses are overlooked for three reasons: 1. the examiner is not thinking about them; 2. filling defects produced by prolapse are confused with those due to a duodenal ulcer or duodenitis; 3. when recognized, no clinical importance is placed on them.

The age incidence is not striking, but Feldman has noted that the majority of his patients were in the fourth decade. Scott, however, found an age distribution of:

20-29 years of age	— 4 cases
30-39 years of age	— 7 cases
40-49 years of age	— 3 cases

The etiology of this condition is as yet unknown, but various theories have been offered. Eliason and Wright believe that a low grade inflammation produces a local hypertrophy of rugae. The hypertrophied folds are further enlarged mechanically by the contractions of the stomach and the pressure of gastric contents by which the folds are lengthened and "pushed along" toward the pylorus. When sufficiently long, they are swept into the duodenum by a peristaltic wave. On the other hand, Rees proposes that a narrowing of the pyloric lumen precedes the actual change in the gastric mucosa, and hyperperistalsis ensues, trying to force gastric contents through the smaller opening. This action loosens the attachment of the mucosa membrane to the muscularis. The mucosa so mobilized, is subject to trauma which leads to hypertrophy, prolapse and later polypoid degeneration. Five cases of Scott's series were operated and there was never any evidence by x-ray, gastroscopy, pathologically, either gross or microscopic, of any gastritis as suggested by Eliason, nor any evidence of a narrowing of the pyloric canal, constriction, or hypertrophy of the pyloric muscle. At

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operation, the prolapsed portion of the gastric mucosa appeared as a loose collar of redundant hypertrophied mucosa that had invaginated into the duodenum and could be forced back into the stomach only to protrude again as a long rosette. The prolapsed folds appeared as normal mucosa, soft and pliable and not fixed, thick or indurated.

Another possible etiologic factor must be considered. A benign peptic ulceration located at the base of the duodenal bulb or in the pre-pyloric area may, in process of healing, produce a local gastritis. This inflammation may lead to a localized hypertrophy of the gastric rugae of the pre-pyloric area which eventually prolapses through the pylorus into the base of the bulb at a time when no other sign of the original ulcer may be present anymore. Melamed's case of prolapse with ulceration of the redundant mucosa makes this theory seem possible. In the normal gastric antrum, the mucosa and muscularis are connected by soft, yielding submucosa composed of loose areolar tissue containing blood vessels, lymphatics, and nerves. This explains a certain limited mobility of the mucosa on the muscularis as found in all normal stomachs and easily demonstrated in autopsy specimens where the mucosa can be moved over the muscularis for 1 to 1½ inches. Scott, in studying over 100 fresh stomachs, states that normally the extent of this movement is not sufficient to permit a prolapse. However, we have witnessed on several occasions that on fresh autopsy material, less than three hours post mortem, one can pull gastric mucosa through the pylorus with a forceps, entering the stomach from the first portion of the duodenum. Enough mucosa could be pulled through to correspond with Scott's description of a small prolapse. This was also attempted on a stillborn and in a stomach greatly dilated from an obstruction; however, in these cases the mucosa was not as mobile as in the normal specimens. A possible explanation for this difference is that the stomach mucosa is exceedingly rapid in its auto-digestion following death, and that Scott's attempts may have been on material a few hours older than ours. If any of our material showed gross signs of post mortem changes, no attempt to mechanically force a prolapse was made.

Forssell, Golden, and Schindler have described active movements of the mucosal folds not related to contractions of the muscularis: for example, during antral systole. Golden noticed that the folds of the mucosa running transversely across the antrum were changed to run in horizontal rows parallel to the long axis of the stomach by moving cephalad and becoming stretched on the muscularis; otherwise as the antrum closes off, the cross folds would be exaggerated, pushed downward and jammed toward the pylorus. The failure of this stretching mechanism may account for herniation of pre-pyloric mucosal folds (Fig. 1).

The muscularis mucosae is known to have muscular activity, independent of that of the main musculature of the stomach. Consequently, it seems possible that neurogenic factors are the inciting cause of a disturbed gastric function that ultimately brings about a mucosal pro-

lapse; for it has been repeatedly shown that emotion such as worry, fear, excitement, and anger, alter gastric function, peristalsis, and chemistry.

The complaints of these patients are varied, depending on the extent and the condition of the prolapsed mucosa, and the symptoms are not so characteristic as to permit a distinct clinical diagnosis. This must be done roentgenographically with the ruling out of other gastrointestinal diseases. The major symptoms listed by Scott are: cramp-like intermittent epigastric pain, relief by food, liquid, but seldom by alkali, sense of fullness, bloating, heartburn, and in fewer instances, nausea and vomiting.

This disorder should be suspected in patients with an atypical ulcer history, in patients that do not make the usual response to an ulcer regimen, in patients with repeated recurrences when placed on solid foods, and in patients with so-called recurrent "functional" complaints. Physical examinations on Scott's patients were essentially negative except the finding of tenderness in the epigastrium on deep palpation. The routine laboratory examinations usually include gastric analysis. Occasionally, one finds occult blood in the stool or other signs of hemorrhage. Gastroscoy failed to positively recognize the folds slipping through the pylorus or to find a consistent hypertrophic gastritis. However, the appearance at fluoroscopy and on the roentgen film is quite characteristic and pathognomonic. The following features of prolapse are noted by Scott and others:

1. The filling defects in the duodenal bulb due to the prolapse are invariably located in the base, immediately around the pyloric opening. The redundant folds produce a central mushroom or cauliflower-like negative shadow.

2. The filling defects vary in size, shape, and appearance during a single examination as well as in repeated examinations, and may even become temporarily reduced.

3. Usually the redundant rugae can be traced from the antral canal through the pyloric opening in the base of the bulb. Visualization of this can be enhanced by exerting moderate compression. A singly prominent gastric ruga is normal and is frequently seen, extending across the pylorus into the bulb (see Fig. 3 a).

4. The bulb is not quick or irritable, in contradistinction to duodenal ulcer or duodenitis.

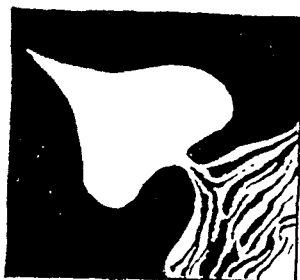
5. Gastric peristalsis is more active and vigorous than in the average patient.

6. No ulcer crater, niches, or incisurae are seen, but Melamed reported one case in which a large ulcer was seen in the prolapsed mucosa and confirmed at operation. Rubin reported a case with proved malignant change in prolapsed polypoid mucosa; therefore, one should look for these conditions.

7. Scott feels that fluoroscopy with serial spot film technique is the examination of choice.

Figure 2 demonstrates schematically various degrees

Fig. No. 1. "Stretching mechanism" of Golden, adapted from W. G. Scott.



A. The rugae are in the transverse position prior to antral systole.



B. During antral systole the folds are stretched longitudinally.

Fig. No. 2. Schematic presentation of various degrees of prolapse.



A. Mild Prolapse



B. Moderate Prolapse



C. Severe Prolapse

Fig. No. 3. Schematic drawings of conditions simulating prolapse.



A. A single ruga entering the base of the bulb is considered normal.



B. A crescent-shaped configuration of the base of the duodenal cap seen in hypertrophied pyloric muscle. The base is smooth and regular. This is not a prolapse.

of prolapse. To illustrate this condition as well as to attempt to correlate the clinical findings we should like to present briefly four cases, two from the clinic and two private patients, that have come to our attention recently. Several other cases have been seen in the last year, but either were not reported on the x-ray sheet, or had other complicating gastro-intestinal conditions.

Case 1. A forty-year-old white male complains of epigastric burning of 10 years' duration, which is non-radiating, and seems to be precipitated by excessive drinking and smoking. The attacks usually are periodic and of one day's duration. They come on about 2 or 3 hours after eating and last one hour. The pain never awakens the patient, but occasionally keeps him from falling asleep. The patient complains of much belching, nausea, and vomiting. He also has had anal discomfort with defecation and rectal tenesmus, and had a hemorrhoidectomy, polypectomy, and excision of an anal ulcer in 1946. Gastric analysis showed free acidity 36 degrees and total acidity of 69 degrees. Stools were guaiac negative. X-ray studies reported a normal upper gastro-intestinal tract, gall bladder, and colon. The stomach emptied in three hours. On re-examination of the x-ray films, a moderate prolapse of gastric mucosa was seen as demonstrated in Fig. of Case No. 1.

Case 2. A forty-three-year-old white female complained of occasional epigastric fullness after meals. The gastric analysis was free acid 20 degrees, and total acidity 55 degrees. The stools were guaiac negative. The x-ray report stated that stomach, duodenum, colon, and gall bladder were normal. The stomach emptied in four hours. Re-examination revealed a small prolapse as seen in Fig. of Case No. 2.

Case 3. A forty-two-year-old white male entered the clinic with the major complaints of dizziness, frontal headaches, tinnitus, and drunken gait. He further complained of much gas and pressure under the left side radiating up into the left arm. This distress occurred one to two hours after meals, and the patient states that he feels better when avoiding cabbage and coffee, and that charcoal gives him active relief. Last year he was told that he had an ulcer and he was treated by diet and powders with temporary relief. His stomach feels better after meals; when it is empty he has a gnawing sensation in the epigastrium which he describes to be different from ordinary hunger pain. E. N. T. consultation diagnosed a possible early Meniere's syndrome and an upper gastro-intestinal x-ray film revealed a moderate prolapse of gastric mucosa. The Ewald meal yielded 54 degrees for free and 80 degrees for total acidity. Stools were negative for blood.

Case 4. A forty-five-year-old white male who had been followed in the chest clinic since 1937 for tuberculosis of the right apex, and in the neurologic clinic since 1940 for epileptiform seizures both of the grand and petit mal types. In January 1947 he came to the gastro-intestinal clinic complaining of belching and bloating for two to three years, which had become worse during the past few months. The patient states that he feels filled up soon after eating, but has no nausea, vomiting, or epigastric pain. Cholecystogram was negative. Ewald 27 degrees for free and 55 degrees for total acidity. Stools were negative. X-ray of the upper gastro-intestinal revealed a small prolapse of gastric mucosa.

In summary, all four cases were over forty years of age; three were males and one female; two were reported as having negative x-rays; only one showed hyperacidity; all stools were negative for occult blood. The prolapses of gastric mucosa were small to moderate and did not require surgery. Under medical manage-

ment all did well. It is remarkable, however, that these prolapses produced distinct clinical symptoms, although none of them could be classified as severe.

DISCUSSION

The most difficult lesions to differentiate from prolapsed gastric mucosa are prolapsed pedunculated tumors and polyps, and this can rarely be done with certainty. The x-ray diagnoses of the 14 cases of Scott were: Gastric ulcer, 1; duodenal ulcer, 11; duodenitis, 2. Papillomata of the duodenum produce filling defects which are larger and not necessarily localized at the base of the bulb. In duodenitis, the bulb is small, irritable, or spastic. The invagination of the base of the duodenal cap seen in hypertrophy of the pyloric muscle lacks the lobulations of the gastric rugae, and is constant in size and shape (see Fig. 3 b). In an attempt to evaluate whether the characteristic roentgenographic appearance of mucosal prolapse in the stomach could be found in normal asymptomatic individuals, Scott studied over 200 sailors with no complaints, and he did not find one pattern that resembled prolapsed gastric mucosa.

The treatment of this condition is medical, and in slight and moderate prolapses frequent small feedings and a bland diet usually afford relief. Hospitalization with rest in bed, relaxation, and freedom from tension, strain, fear, and worry brings about definite improvement. Condiments, such as tobacco, alcohol, and caffeine should be eliminated. Mild sedation is often of great value. It is apparent, that the therapy is the same as that for peptic ulcer. Therefore, it is possible, that small unrecognized ulcers lead to prolapse of the mucosa. On the other hand, prolapses may be due to other factors which play a role in peptic ulcer, as mentioned above. Surgery is indicated in the case of large prolapses. These always produce symptoms and usually are resistant to medical management; they may develop large or repeated small hemorrhages, and they may produce partial obstruction with retention of gastric contents. As it was a military necessity to rehabilitate Scott's cases as rapidly as possible, surgery was performed in five cases or 36%, with complete relief of symptoms and no recurrence on a full diet. Rees recommends an antral gastrectomy, excision of the redundant mucosa, anchorage of the mucosa to the muscularis, and sectioning of the pyloric muscle. French resected the redundant mucosa and performed a Heineke-Mickulicz pyloroplasty.

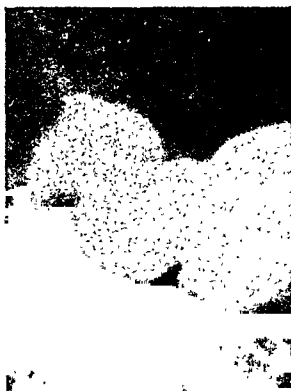
Two cases of transpyloric prolapse of redundant gastric mucosa were operated successfully by MacKenzie with resection of the prolapsed fold and closure by a pyloroplasty. His indications for surgery were equivocal x-ray findings with difficulty in differentiating from polyps, continued bleeding, and evidence of pyloric obstruction. Before advising surgery one should consider the complications of even a pyloroplasty with subsequent ulceration at the suture line, especially when done in the presence of hyperacidity.

This review has been presented because of a feeling

that prolapse of redundant or hypertrophied gastric mucosa into the duodenum is a definite clinical entity which has been disregarded, and further study to evaluate this disorder should be made. As in all medical conditions, the proof of definite pathology lies with the radiologist, surgeon, or pathologist. The radiologist

should look for such cases, especially when there is a clinical picture of ulcer and no definite roentgenographic evidence. In small prolapses, repeated x-ray studies should be made, as the mucosal pattern varies from time to time, a prolapse even becoming temporarily reduced. Suspicious cases should be reported to the

Case No. 1. Forty-year-old male complaining of epigastric burning of ten years duration.



A. Duodenal cap shows a moderate "cauliflower" filling defect at the base.



B. Another view of the same cap demonstrating a little less severe prolapse.

Case No. 2. Forty-three-year-old white female with vague epigastric distress.



A.



B.

A. Small prolapse is seen at the base of the bulb, while in view B of the same patient no definite prolapse can be seen.

Case No. 3. Forty-two-year-old white male complaining of much gas and pressure coming on one to two hours after meals. Gastric analysis showed hyperacidity.



A Moderate prolapse seen at base of the duodenal cap which on subsequent views at different angles assumes the characteristics of a small prolapse (B and C).

Case No. 4. Forty-three-year old white male with belching and bloating for two to three years



A The variations of prolapse are seen in different views on the same patient, a small prolapse is seen in A and C, while B shows a normal lumen

internist for evaluation and medical management. We believe that the complications warranting surgery, as previously listed, are few and that surgical statistics will be rare. Although the pathologist almost never has to rule out this condition as a cause of death, he may aid further statistical study by looking for prolapses at autopsies.

SUMMARY

A review of the literature on prolapsed hypertrophied

or redundant gastric mucosa is presented and four cases are reported.

It seems that prolapsed gastric mucosa is more frequent than hitherto assumed, and that it is capable of producing symptoms even in cases of small or medium prolapses. The symptoms are amenable to simple medical management. Therefore, more attention should be directed toward the recognition of prolapse and toward the clinical evaluation of its symptoms.

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Perforation of the Gall Bladder

By

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and

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IN SPITE of the fact that much has been written about calculous gall bladder disease, many preventable and needless deaths still occur from the complications of this disease.

Cholecystitis and cholelithiasis of long duration, even if not associated with colic (silent stones), may nevertheless lead to various complications. One of the most serious complications is perforation of the gall bladder. Perforation may occur into the peritoneal cavity with resulting pericholecystic abscess or bile peritonitis; or perforation may occur into a viscus leading to the formation of an internal biliary fistula.

Deaths from uncomplicated biliary tract disease are rare and even the elective surgical procedures carry a very low mortality. People frequently die, however, from complications which develop as a result of long

standing calculous biliary tract disease, which has either not been diagnosed early enough, or which if diagnosed correctly, was not treated by surgery because of the mildness of the symptoms.

Many cases of calculous gall bladder disease are still not operated upon, in spite of the fact that the majority of clinicians are in general agreement about the necessity of surgery in this condition. The reasons for this can be ascribed to both the patients and the doctors. Patients refuse operations for a variety of reasons, while frequently the doctors themselves are undecided about the indications for surgery. In many instances, when the patients refuse operation because of lack of colic, the physician will acquiesce by not adequately stressing the dangers of non-operation. This is usually due to the erroneous idea that "silent" gall stones are innocuous and that patients must have repeated attacks of pain and distress before surgery is indicated.

The purpose of this paper is to discuss one of the frequent complications of calculous gall bladder disease, namely, perforation of the gall bladder, and to stress

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the need for surgery in calculous gall bladder disease as a prevention of future complications.

INCIDENCE

Gangrene and perforation of the gall bladder is not unusual, even in non-calculous gall bladder disease. It occurs more frequently following attacks of acute cholecystitis than one generally realizes. Thus Cowley and Harkins (1) state that in a collected series of 2,261 cases of acute cholecystitis, perforated gall bladder occurred in 13 per cent of the cases. They also reported that in a total of 433 perforated gall bladders, the average mortality was 20.8 per cent. Hicken and Coray (2) reported that the incidence of gall bladder perforation in their series of cases of acute cholecystitis was 25 per cent. Heuer (3) concluded from his review of the literature that gangrene and perforation of the gall bladder occurred in 20 per cent of the cases of acute cholecystitis in which the pathologic process was not interrupted by surgical treatment. That perforation of the gall bladder is a serious condition can be further seen by Heuer's review of the experiences of fourteen authors in which he cites five hundred cases of perforation, showing that the mortality varied between 15 and 65 per cent, averaging 45 per cent. In comparing the incidence of gangrene and perforation of the gall bladder with that of the appendix, Heuer (3) found an incidence of 15.7 per cent in acute conditions of the gall bladder and 17.5 per cent in acute appendicitis. Hotz (4) concluded from his investigations that the incidence of peritonitis associated with perforations of the gall bladder was found to rank as high as that of peritonitis associated with the acute perforations of the appendix. The incidence of the latter was reported by McClure and Altemeier (5) as 53 per cent in their series of cases.

Johnstone and Ostendorph (6) reviewed 12,000 consecutive routine necropsies at the Los Angeles County Hospital from April 1936 to January 1942 and found 32 instances in which perforated gall bladder was found to be the cause of death, or an incidence of one death due to perforation among every 375 which came to autopsy.

Internal biliary fistulas, the result of perforated gall bladders, are infrequent but still less commonly diagnosed preoperatively. Donald et alia (7) in a recent review, report that the literature contains only 108 cases of preoperatively diagnosed internal biliary fistulas. At operation, or postmortem the findings of internal biliary fistulas are more frequent. Courvovsier (8) reported an incidence of 4.8 per cent in patients dying from gall bladder disease during a six years period. Dean (9) found them in 1.2 per cent of his gall bladder cases, while Puestow (10) encountered 16 cases of internal biliary fistulas in 500 operations for benign biliary tract disease. All agreed that infection and calculi in the biliary tract are responsible for production of the greatest number of these fistulas.

In a review of post mortem material of biliary tract disease in the Cook County Hospital during the past 13 years—1932-1945, 45 instances of perforated gall bladder were found. Of these 45 cases, 35 had recent

gall bladder perforations with associated complications, as the immediate cause of death. Ten patients had ancient perforations in the form of cholecystogastric or cholecysto-duodenal fistula (7 into duodenum and 3 into stomach) which were discovered upon post mortem as an incidental finding and which were not the immediate cause of death.

Seventeen of the forty-five patients in our series, or thirty-eight per cent, were males; a finding in confirmation of that of others. Thus, of the reported cases of perforated gall bladder, the males represented 36% in Cowley and Harkins (1) series; 52% in Sander's (11), 31% in Judd and Phillips' (12) and 40% in Stone and Douglas' (13) series.

This comparatively high incidence of perforated gall bladder in the male is of rather astonishing interest because of the current, general belief that gall bladder disease is a very rare occurrence in the male and that usually only patients who fall into the "fat, fair, forty, fecund" class are subject to this disease.

TABLE I

Sex and color of forty-five cases in whom perforated gall bladders were found at necropsy.

SEX	COLOR	NUMBER	PER CENT
Male	Colored	1	2
	White	16	36
Female	Colored	6	13
	White	22	49
TOTAL		45	100

Only seven of the 45, or approximately 15% of the cases were colored. This percentage is somewhat according to the common concept of gall bladder disease rarely occurring in the negro. (Table I).

Forty of the 45 cases with gall bladder perforations, or approximately 90 per cent, were aged fifty years and over. No perforations occurred in males under 50 years of age, but did occur in 17% of the females. This finding is in accord with other reports that most gall bladder perforations occur in people of the higher age group, especially so in the male. Cowley and Harkins (1) stated that 60% of their cases occurred in people over the age of fifty. The average age reported by Schaeffer (14) was fifty-nine years. Judd and Phillips (12) reported that the majority of their patients were more than 50 years of age. In Stone and Douglas' (13) series, the average age of the patients was 52 years. (Table II).

Forty-one or 91% of our 45 cases of perforated gall bladder had stones either in the gall bladder or common bile duct. Thirty-eight or 85% of the 45 cases of ruptured gall bladder had evidence of chronic cholecystitis. This is in agreement with Cowley and Harkins' (1) review of 22 perforated gall bladders in which stones were reported in 92% and chronic cholecystitis in 27% of the cases. Judd and Phillips (12) reported that gall stones were present in 56 or 92% of their 61 cases, while Sanders (11) found stones in 42 or 91% of his 46

cases of perforated gall bladders. All of Schaeffer's (14) 20 cases, with one possible exception, had gall stones. These data point quite clearly to the pre-disposing role which gall stones play in rupture of the gall bladder and formation of internal biliary fistulas. (Table III).

TABLE II

Age and sex of forty-five cases in whom perforated gall bladders were found at necropsy.

AGE	MALE	FEMALE	TOTAL
Under 40	0	2	2
40 - 49	0	3	3
50 - 59	8	7	15
60 - 69	4	9	13
70	5	7	12
	17	28	45

CLINICAL MANIFESTATIONS (Table IV) HISTORY OF PREVIOUS GALL BLADDER ATTACKS

In only 11, or 32% of our series, was a previous history of gall bladder disease elicited. This incidence is small compared to Cowley and Harkins (1) who report that over 90% of their 25 cases of perforated gall bladders complained of previous gall bladder disease. Practically all of Stone and Douglas' (13) cases gave a history of pre-existing chronic cholecystitis. Eliason and McLaughlin (15) state that in all but one of their

TABLE III

Additional post mortem findings in forty-five cases of recent and ancient perforated gall bladders* found at necropsy.

POST MORTEM FINDINGS	NUMBER	PER CENT
Chronic Cholecystitis	38	85
Cholelithiasis and Choledocholithiasis	41	91
Peritonitis	20	44
Ruptured Gall Bladder	13	29
Cholecysto-entero-enterostomy	11	24
Peri Cholecystic Abscess	8	17
Ascending Cholangitis and Cholangiolitis	7	15
Gangrene Gall Bladder	5	11
Empyema Gall Bladder	5	11
Sub-phrenic abscess	5	11
Liver Abscess	4	9
Stone Cystic Duct	2	5
Biliary Cirrhosis Liver	2	5
Hemorrhagic Pancreatitis	1	2

*Gall bladder perforation was considered at post mortem by the presence of rupture as such, by gangrene, or empyema with pericholecystic abscess, sub-phrenic abscess, or peritonitis, or internal biliary fistula.

nine cases, a definite history of previous attacks of cholecystitis could be elicited, the duration of symptoms ranging from 18 months to 15 years, and averaging six years. Only three of the 20 patients with perforation of the gall bladder reported by Schaeffer (14) complained of symptoms for less than one year. In his series the duration of symptoms varied from two weeks to 35 years, but the majority of cases were of long duration.

SYMPTOMS AND SIGNS

Abdominal pain (97%) and vomiting (70%) were the commonest symptoms in our group. Cowley and Harkins' (1) found that nausea, usually with vomiting and persistent pain in the right upper quadrant of the

abdomen were the commonest symptoms. Stone and Douglas (13) also reported that all of their cases had pain as their main complaint. Right upper quadrant tenderness was present in 43%, and generalized tenderness was found in 34% of our cases. Right upper quadrant rigidity was present in 31 and generalized rigidity

TABLE IV

Clinical findings in thirty-five cases in whom a ruptured gall bladder was found at necropsy, (excluding 10 cases of biliary fistula).

	MALE (16)	FEMALE (19)	TOTAL (35)	PER CENT
Previous history of				
Gall Bladder disease	5	6	11	32
Abdominal pain	16	18	34	99
Vomiting	12	14	26	70
Abdominal tenderness,				
generalized	6	6	12	34
Right Upper Quadrant				
tenderness	7	8	15	43
Rigidity, generalized	5	3	8	23
Right Upper Quadrant				
rigidity	5	6	11	31
Jaundice	4	4	8	23
Peritonitis generalized	6	4	10	29
Right Upper Quadrant mass	3	0	3	1

in 23% of the cases. Twenty-three per cent had evidence of jaundice. Cowley and Harkins (1) reported right upper quadrant tenderness in 96%, generalized abdominal tenderness in 28%, and jaundice in 20% of his cases. Schaeffer (14) found jaundice in 20% of his cases. Stone and Douglas (13) observed jaundice in 35% of their 17 cases.

TABLE V

Ante-mortem clinical diagnosis in forty-five cases in whom gall bladder perforation was found at necropsy.

DIAGNOSIS	MALE	FEMALE	TOTAL
Intestinal Obstruction	4	5	9
Hypertensive Heart Disease	0	5	5
Acute Cholecystitis	1	3	4
Hepatitis	2	0	2
Pneumonia	1	1	2
Perforated Peptic Ulcer	2	0	2
Hemiplegia	1	1	2
Cirrhosis of the Liver	0	2	2
Choledocholithiasis	0	2	2
Carcinoma of Gall Bladder	0	2	2
Peritonitis	1	0	1
Metastatic Carcinoma	1	0	1
Bleeding Peptic Ulcer	0	1	1
Empyema of Gall Bladder	0	1	1
Pancreatitis	0	1	1
Hydrops of Gall Bladder	1	0	1
Umbilical Hernia (strangulated)	0	1	1
Coronary Heart Disease	1	0	1
Pernicious Anemia	0	1	1
Carcinoma of Rectum	1	0	1
Carcinoma of Liver and Bile Ducts	1	0	1
Diagnosis Deferred	0	2	2

DIAGNOSIS

Only 10 of the 45 cases, or 22%, were diagnosed as having some type of biliary tract trouble prior to death. The correct diagnosis of perforated gall bladder was not made in a single instance prior to death. The other 35 cases had a variety of diagnoses, the most common being intestinal obstruction and acute cholecystitis. It

can be seen why this is so, for the patients had abdominal pain, vomiting, tenderness and rigidity of the abdomen. (Table V).

Among the 45 cases there were 28 females and 17 males. Eight, or 32% of the females were diagnosed as biliary tract disease; while only two or 12% of the males were diagnosed as having biliary tract disease. (Table VI). The most common mistaken diagnosis among the men was intestinal obstruction (4 cases), perforated peptic ulcer (2 cases), hepatitis (2 cases), and one each of the following: coronary thrombosis, pneumonia, and peritonitis.

TABLE VI

Ante-mortem diagnosis of biliary tract disease in 10 of 45 cases in whom a perforated gall bladder was found at necropsy.

DIAGNOSIS	MALE	FEMALE	TOTAL
Acute Cholecystitis	1	3	4
Cholelithiasis	0	2	2
Carcinoma of Gall Bladder	0	2	2
Empyema of Gall Bladder	0	1	1
Hydrops of Gall Bladder	1	0	1
TOTAL	2	8	10

Four of the above ten cases were operated; one male (Hydrops of Gall Bladder) and three females (one with Empyema of Gall Bladder, and two with Common Duct Stones).

Cowley and Harkins (1) found that only 12% of their cases were correctly diagnosed as perforated gall bladder. Sanders (11) reported that a correct pre-operative diagnosis was made in only 9% of his 46 cases of perforated gall bladder.

DISCUSSION

Our study shows that 91% of the 45 cases of perforated gall bladders had stones either in the gall bladder or common duct and that 85% of the cases had evidence of chronic cholecystitis. These findings are in accord with other reports in the literature as cited above and present added evidence for the theory that stones and/or chronic infection are the predisposing and underlying factors in perforation of that viscus. Disease of the biliary tract—especially if calculous—whether associated with recurrent attacks of biliary colic or whether temporary asymptomatic, will produce pathological changes of a chronic irreversible nature which will have serious consequences at a later date. Gall stones, when present, start a progressive pathological process which, as it progresses, calls forth additional and more serious complications. A vicious cycle begins, for the longer the process operates, the more possible complications, the older the patient, the poorer the surgical risk and the higher the mortality.

Glenn and Moore (16a) have described two mechanisms responsible for perforations in acute cholecystitis. One is that gangrene of the wall of the gall bladder may often result from changes that take place in the organ during an attack of acute cholecystitis. These changes

most frequently encountered at operation consist of a stone impacted in the ampulla of the gall bladder, edema of the wall, blockage of the lymphatics, obstruction to the venous return by direct pressure upon the vessels or by thrombosis, and in some instances, arterial occlusion.

The second mechanism of perforation they believe to be also associated with infection and calculi. In this instance, however, the infection is more insidious, involving mainly the Rokitsansky-Aschoff sinuses. The latter may enlarge into actual diverticula. These may empty their purulent contents into the gall bladder itself or may rupture into one of the neighboring organs (liver, intestine) or into the free peritoneal cavity.

Our series, as well as those of others, has shown that the diagnosis of perforated gall bladder is made infrequently. It is a difficult diagnosis to make, even for those with marked diagnostic acumen. Glenn and Moore (16a) in a review of their total experience concluded that they were unable to distinguish acute cholecystitis, acute cholecystitis with gangrene, and perforation which has resulted in a walled-off abscess. They further state that "free perforation into the peritoneal cavity of a gangrenous gall bladder is rarely recognized early enough to save the patient's life."

Judd and Phillips (12) in discussing perforations of the gall bladder believe that the severity of the symptoms does not always indicate the extent of the pathological process. Thus in some instances, the disease may progress to the stage of perforation and abscess formation without producing acute pain or other abdominal disturbances. Eliason and Stevens (16-b) conclude that in cholecystitis one cannot prognosticate the severity of the pathological condition. The latter cannot be safely estimated by any physical or laboratory tests available at the present time. Wallace and Allen (17) state that empyema and gangrene are potent factors in the causation of rupture of the gall bladder, and that with conservative treatment, even under careful observation in a hospital, gangrene with perforation cannot be anticipated and frequently progresses to a dangerous stage. This is supported by Cowley and Harkins (1) and by Sanders (11) who found that only 12 and nine per cent of their cases, respectively were correctly diagnosed as perforated gall bladders. Our own experience corroborates these findings. None of the 45 cases in our series was diagnosed as such before death.

The relationship between perforation of the gall bladder and chronic cholecystitis, gangrene, and calculi has been definitely established. It is also unanimously agreed that it is difficult to make a correct pre-operative diagnosis of perforation or of any of the complications leading to perforation of the gall bladder. It seems therefore illogical to delay surgery in proven gall bladder disease. Yet delay occurs not infrequently. The question therefore arises, what or who is responsible for this dangerous state of affairs?

The first responsibility rests with the patient. The latter will often refuse an operation as soon as he recovers from the acute attack and feels better, and even more so if he has only mild symptoms or is asymptomatic—gall stones having been found accidentally.

The second and at times main responsibility rests with the doctor, who fails to impress the patient strongly enough with the dangers of delay of operation. On the assumption that the severe biliary symptoms represent only another attack of acute cholecystitis which will subside as the previous ones have subsided, cases with gall bladder disease are permitted to progress beyond a point when surgery can offer much help. Progress in surgical technique has reduced operative mortality to as low as 0.5 per cent in uncomplicated gall bladder surgery. Delay in surgery, however, leads to higher mortality. Graham (18) aptly illustrated the dangers of procrastination by citing operative mortality figures for cholecystectomy. Thus if operation is performed after two attacks, the mortality is 2 to 3 per cent; after three or more attacks it is 8 to 9 per cent; in the presence of jaundice, 10 to 12 per cent; and in the presence of pancreatitis nearly 50 per cent. Hence to procrastinate is to invite trouble, and the attending physician should therefore use all his persuasive powers to convince his patients about the necessity of surgery while their gall bladder disease is quiescent. An interval cholecystectomy early in the course of the disease will prevent the progressive and irreversible pathological process which may end in gangrene and perforation.

One of the reasons why doctors do not persuade these patients more frequently to be operated is the uncertainty in their own minds as to the indications for gall bladder surgery. There still exists in the minds of some the fallacious assumption that the so-called asymptomatic, or silent type of stone or stones, is harmless and that the mere presence of stones in the biliary tract is no indication for surgery unless the patient has repeated attacks of colic. This assumption has been, it is believed, a source of much misunderstanding and has caused much suffering in some instances.

We believe that stones in the gall bladder are an indication for surgery, regardless of whether symptoms are present or absent. Another indication for surgery is non-visualization of the gall bladder in the presence of colic, and absence of jaundice. One should not expect to see gall stones on every x-ray film before advising operation for biliary tract disease. Some gall stones are soft and do not give a calcific shadow. These appear only as radiolucent shadows within a gall bladder which is at least partially outlined by the ingested dye. If for one or more reasons, dye has not entered into the gall

bladder, the soft stones will remain invisible. In cases of repeated colics with a non-visualization of the gall bladder on repeated examination in spite of absence of jaundice, operation is urgently indicated.

How then are we to prevent the occurrence of complications in gall bladder disease? Prevention of complications can be accomplished in two ways; first, by proper diagnosis of gall bladder disease followed by appropriate surgery when the indications, as discussed above, exist. Secondly, by making physicians aware of the dangerous complications of chronic gall bladder disease so that they may first, be more persuasive with their procrastinating patients, and secondly, more promptly and accurately diagnose perforation and perform immediate treatment. The physician should keep such a possibility in mind whenever he meets a patient usually over the age of 50 with a severe gall bladder attack, and who is not relieved by the usual palliative therapy within a reasonable period of time. Furthermore, he should remember that 30 to 50 per cent of perforated gall bladders occur in the male, in whom the diagnosis of acute biliary tract disease is usually made infrequently, because of an apparent misconception that gall bladder disease is a "female" malady.

SUMMARY

1. The incidence of perforated gall bladders is higher than usually assumed, varying from 13-25 per cent of acute gall bladder conditions.
2. Chronic cholecystitis and cholelithiasis are underlying factors in the production of gangrene and subsequent perforation of the gall bladder.
3. Gall bladder perforations occur most commonly in persons aged 50 and over.
4. Males are affected more frequently than is generally thought; 38 per cent in our series.
5. A very small per cent of perforations are diagnosed correctly or early enough to save the patient's life. None of our series was correctly diagnosed prior to autopsy.
6. The reasons for delay in surgery in definite gall bladder disease are first, procrastination by patients and acquiescence to this by their physicians, and secondly, uncertainty in the minds of some physicians as to the indications for gall bladder surgery.
7. The indications for gall bladder surgery are outlined.

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The Influence Of An Antacid (Nonreactive Aluminum Hydroxide Gel) On Evacuation Of The Bowels And The Fecal Column.

(Introducing A Standardized Method For the Clinical Study Of Constipating Effects Of Drugs)*

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INTRODUCTION

THE USE of antacids in the treatment of peptic ulcers is generally accepted. However, there is variation in the antacids employed and the diets prescribed. There is every indication that until the etiology of peptic ulcers is established the treatment will continue to vary from time to time. The employment of protein hydrolysate has been recommended (1) and widely used in recent months. Its ability to regenerate tissue at the ulcer site still remains to be proven. There is strong indication that protein hydrolysate will probably be used primarily for its nutritive value.

Colloidal aluminum hydroxide is an effective antacid generally accepted as reacting chemically to neutralize the gastric hydrochloric acid. There are, however, those (2) (3) who believe aluminum hydroxide gel absorbs the hydrochloric acid and since that is a physical means refer to the drug as being nonreactive. Aluminum hydroxide gel according to N. N. R. (4) is reactive. The aluminum hydroxide gel under study (**) is, according to the manufacturer, nonreactive. We shall not, at this time, enter into a discussion of the merits of reactive and nonreactive aluminum hydroxide gel. Further, its antacid effect is sufficiently established so as not to require repetition.

FORMULAE

This study was made for the purpose of determining whether or not constipation resulted from the use of the antacids in question. Three formulae were used and neither the patients or the authors knew, at the time of study, what the ingredients were other than that each had antacid qualities. The formulae were num-

bered 1, 2 and 4. Number one was a liquid, each tablespoonful of which contained fifteen grains of non-reactive aluminum hydroxide gel, thirty grains of magnesium trisilicate and a trace of calcium phosphate. An equal amount of formula number two contained fifteen grains of N. N. R. reactive aluminum hydroxide, thirty grains of magnesium trisilicate and a trace of calcium phosphate. The last formula, number four, contained fifteen grains of nonreactive aluminum hydroxide, a trace of calcium phosphate, but no magnesium trisilicate in each tablespoonful.

PRECAUTIONS

Every feasible precaution was taken to avoid constipating effects from medications or diets. During the entire course of study the patients were to abstain from any and all other medications. Each patient was placed on the diet listed in Table I. The patient remained on that diet for one week before taking the first formula, during each two-week period while on the respective formula and for one week between changes to each succeeding formula. Enemata or any other procedures that would artificially cause bowel evacuation were prohibited. Six patients, who are not included in our reported group, were disqualified for a breach of cooperation. Standardization was insisted upon so that even if constipation was present before this experiment the drugs under study would each have the same basic standards to work on. We are, therefore, justified in the assumption that if the number of bowel movements or the character of the feces is altered the formula in question would be responsible.

DOSAGE

The dose of the formulae under study was always

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Table No. I—Standard Diet that each patient was obliged to follow throughout the course of study.

BREAKFAST:		Cooked cereal: strained oatmeal, cream of wheat, farina, hominy, wheatena, with cream and a little sugar.
	<i>Bread:</i>	white bread — oven-made toast with butter.
	<i>Beverage:</i>	Kaffee Hag or Sanka coffee with cream and sugar as desired.
10:00 A. M.:		Toast, Holland rusk, zweibach with butter. Ovaltine made with water and a little cream added to taste.
DINNER:		<i>Creamed soups:</i> Chicken or any fowl except duck or goose, lamb chop or roast lamb, ham, broiled tender beef steak or roast beef.
	<i>Meat:</i>	
	<i>Fresh fish:</i>	
	<i>Vegetables:</i>	Baked, boiled or mashed potatoes. Rice, macaroni, spaghetti, vermicelli, noodles (with butter added at the table or a little chicken gravy or tomato or mushroom sauce.) Spinach, carrots, stringbeans, peas, small lima beans, celery, squash, tender young onions, beets, beet greens, asparagus tips.
	<i>Bread:</i>	Toast with butter.
	<i>Dessert:</i>	Rice, sago, tapioca, farina, or bread pudding, custard, junket, plain gelatin with cream.

4:00 P. M. Same as at 10:00 A. M.

SUPPER: Same as at breakfast.

the same, one tablespoonful in one-half glass of water taken one-half hour before breakfast, one hour after lunch and before retiring. We were cognizant of the fact that the dosage was quite large. Each formula was used for two weeks so that every opportunity for it to have a constipating effect be given to the respective formula. As previously mentioned, a one-week period during which time only the standard diet was used, was allotted between changes to the next succeeding formula. This was for the purpose of eliminating the preceding formula from the bowel and permitting the bowel to reestablish itself as when originally only on the standard diet.

CONSTIPATION

There is considerable variance in the laity's interpretation of constipation. Questioning some patients as to their interpretation we found that some thought that they were constipated if they had less than two daily bowel movements. Others thought that if the first fecal segment was hard the patient was constipated. A few replied that if the feces were formed and not mushy they were constipated. The majority said that if the bowels did not move once or more often in twenty-four hours that would mean constipation had developed.

Constipation has been given varying definitions by different authors (5) (6) (7). Bowel evacuation is influenced by the length of the gastrointestinal tract (8), by the food ingested, by emotional reactions, etc. If there is a sensation of incomplete evacuation of the bowels and/or the period between evacuations becomes prolonged, we believe that a patient is constipated. However, should there be a distinct organic defect involving the colon in conjunction with the constipation, then the condition had best be referred to as obstipation.

Since there is such variance of opinion as to what is

the definition for constipation, we decided that we would report on the changes in the frequency of bowel movements, formation of feces and consistency of same from the standard diet alone to those when each formula was used in conjunction with the diet.

REPORT

The patients studied were thirty-five unselected cases from the Gastrointestinal Clinic (O.P.D.) of the Queens General Hospital. The diagnosis of each of the patients studied is as listed in Table II. That table also lists the results obtained in each individual case. Table III summarizes the findings on all of the patients with each antacid and the standard diet used in the study.

From Table III note that:

(a) Using the standard diet without any antacid for one week the thirty-five patients had an average of 8.1 bowel movements during that week. Further, 85.7% of patients had formed feces while 5.7% had mushy feces. The consistency of the feces was hard in 25.7% of patients and soft in 48.6%.

(b) When formula No. 1 was used in conjunction with the standard diet, the average number of bowel movements increased by .2 during the first week and .6 during the second week of study as compared to the results with only the standard diet. Using the same basis, the feces were less frequently formed in 8.6% of patients during the first week and 17.1% during the second week. The consistency of the feces remained unchanged.

(c) Once again, using the results with only the standard diet as a basis it was found that when formula No. 2 was added the average number of bowel movements was, however, decreased by .3 and .4 respectively during the two-week study period. The percentage of patients having formed stool, remained constant but the consistency of the feces became harder in 5.7% of the patients during the first week and in 25.7% of patients during the second week.

(d) When formula No. 4 was used in conjunction with the standard diet, the average number of bowel movements decreased .2 and .5 respectively during the two-week study period in comparison to the average number of bowel movements when only on the standard diet. The percentage of patients having formed feces increased 2.9% and 5.7% respectively. The feces became hard in 5.7% more of patients during the first week and in 17.1% more during the second week.

CONCLUSION

Upon examining Table III we find that in listing the shape of the feces, there was a decrease in the number of formed feces after using Formula I and the standard diet, as compared with the standard diet alone. These findings were more marked in the second week as compared with the first week. With Formula II, the number of formed feces remained constant and with Formula IV, there was an increase slightly more marked in the second week. Upon examining the statistics for consistency of the feces in the same table, we find that the number of hard feces remained constant with

No.	Clinical Diag- nosis	1st wk st'd diet		1st wk st'd diet & P 1		1st wk st'd diet & P 2		1st wk st'd diet & P 4		2nd wk st'd diet & P 1		2nd wk st'd diet & P 2		2nd wk st'd diet & P 4	
		No. bowel movements	Shape of feces Consistency of feces	No. bowel movements	Shape of feces Consistency of feces	No. bowel movements	Shape of feces Consistency of feces	No. bowel movements	Shape of feces Consistency of feces	No. bowel movements	Shape of feces Consistency of feces	No. bowel movements	Shape of feces Consistency of feces	No. bowel movements	Shape of feces Consistency of feces
1	Chronic gastritis	8 F S		7 F S		7 F S		7 F H		7 F S		7 F H		9 F H	
2	Post-op per- forated duo- denal ulcer	11 F H		11 F H		11 F H		12 F H S		11 F H		12 F H		11 F H	
3	Diverticulo- sis of colon	6 F S		7 F S		5 F S		4 F H		6 F S		6 F H		5 F H	
4	Diarrhea	27 M S		19 M S		25 M S		21 F S		25 F S		17 F H S		17 F S	
5	Biliary dyskinesia	6 F H		6 F H		5 F H		6 F S		6 F H		4 F H		7 F H	
6	Chronic gall bladder stones	7 F S		8 F S		7 F H		9 F S		9 F S		8 F H		6 F S	
7	Chronic gastritis	12 F S		16 F S		14 F S		10 F S		13 F S		11 F S		8 F S	
8	Peptic Ulcer	5 F S		6 F S		6 F S		6 F S		8 F S		8 F S		6 F S	
9	Duodenal ulcer	4 F S		3 F H		3 F H		2 F H S		0 0 0		3 F H		3 F H	
10	Chronic gall bladder	6 F S		5 F S		5 F S		7 F S		6 F S		6 F S		6 F H	
11	Chronic gall bladder	13 M S		16 M S		17 M S		17 M S		18 M S		13 M S		16 M S	
12	Chronic gall bladder	7 F S		5 F S		7 F S		8 F S		4 F H		10 F S		8 F S	
13	Post op.abd. adhesions	7 F S		9 F S		7 F S		4 F H		10 F S		6 F H S		4 F H	
14	Spastic colon	8 F S		8 F S		9 F S		9 F S		9 F S		10 F S		7 F S	
15	Gastric ulcer	5 F S		5 F S		7 F S		7 F S		7 F S		7 F S		7 F S	
16	Biliary dyskinesia	9 F S		7 F H		12 F H		8 F H		9 F H S		15 F H		6 F H	
17	Chronic Arthritis	12 F H S		11 F H S		5 F H		5 F H		11 F H S		6 F H		5 F H	
18	Spastic colon	7 F S		7 F S		7 F S		7 F S		9 F S		8 F S		7 F S	
19	Prepyloric ulcer	5 F H		7 F H		6 F H		5 F H		8 F H		4 F H		3 F H	
20	Duodenal ulcer	8 F S		11 M S		16 F S		16 F S		9 F S		12 F H		20 F S	
21	Duodenal Ulcer	4 F H S		7 F S		6 F S		6 F S		8 F S		5 F S		6 F H S	
22	Chronic constipation	2 F H		2 F H		1 F H		1 F H		2 F H		2 F H		2 F H	
23	Duodenal ulcer	14 F H		14 F H		14 F S		13 F H		14 F H		16 F H		12 F H	
24	Diverticulo- sis of colon and gall stones	7 F S		10 F S		7 F H S		7 F S		10 F S		6 F H		7 F H S	
25	Marginal ul.	6 F H		6 F H S		5 F H		5 F H		7 F S		5 F H		5 F H	
26	Duodenal ul.	5 F H		7 F S		4 F H		10 F S		9 F S		3 F H		6 F S	
27	Duodenal ul.	7 F S		6 F S		8 F S		7 F S		5 F S		7 F S		5 F S	
28	Duodenal ul.	7 F S		9 F H S		7 M S		7 M S		8 F H S		7 F H S		7 M S	
29	Duodenal ul.	6 F H		10 F S		8 F H S		9 F S		14 F S		9 F S		8 F H	
30	Enteroptosis	6 F S		5 F S		6 F S		9 F S		8 F S		6 F H		5 F S	
31	Gastroptosis	9 F S		10 F S		7 F S		6 F S		7 F S		7 F S		7 F S	
32	Chronic constipation	12 F S		17 F S		13 F S		17 F H		15 F S		14 F S		17 F H	
33	Chronic gall bladder	5 F S		7 F S		3 F H		5 F H		8 F H		3 F H		6 F H	
34	Chronic constipation	3 F H		3 F H		2 F H		3 F S		2 F H		3 F H		4 F H	
35	Chronic constipation	7 F H		4 F H		3 F H		3 F H		5 F H		2 F H		3 F H	

TABLE No. II—SUMMARY OF EXPERIMENTS CONDUCTED IN THIS STUDY.

Key to above symbols:

H—hard S—soft F—formed M—mushy

F/H—formed more often than mushy.
F/M—formed as often as mushy.
S/H—soft more often than hard.
S't'd diet—Standard diet.

M/F—mushy more often than formed.
H/A/S—hard as often as soft.
H/S—hard more often than soft.

The shape and consistency mentioned indicates that the same existed 2/3 or more times in the number of bowel movements under consideration. If less than 2/3 times, the recording is as follows: F/M or M/F — or H/S or S/H. For example: 9 F/H Patient had 9 bowel movements, of which 6 were formed and hard. 9 F/M—H/S Patient had 9 bowel movements of which 5 were formed and hard.

TABLE NO. III

Routine Used For Study	Number of			Shape of feces										Consistency of feces									
	Bowel Movements			F		M		F		M		Had no b.m.		H		S		H		S		Had no b.m.	
	Max- imum	Mini- mum	Aver- age	Patients		Pt's		Pt's		Pt's		Pt's		Pt's		Pt's		Pt's		Pt's		Pt's	
				No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Standard Diet - (1 wk)	27	2	8.1	30	85.7	2	5.7	3	8.6	0	0	0	0	9	25.7	17	48.6	4	11.4	4	11.4	1	2.8
Standard Diet and B 1 - (first week)	19	2	8.3	27	77.1	2	5.7	5	14.3	1	2.8	0	0	9	25.7	17	48.6	4	11.4	5	14.3	0	0
Standard Diet and B 1 - (second week)	25	0	8.7	24	68.6	1	2.8	9	25.7	0	0	1	2.8	9	25.7	20	57.1	2	5.7	1	2.8	2	5.7
Standard Diet and B 2 - (first week)	25	1	7.8	30	85.7	0	0	1	2.8	4	11.4	0	0	11	31.4	14	40.0	7	20.0	3	8.6	0	0
Standard Diet and B 2 - (second week)	17	2	7.7	30	85.7	1	2.8	4	11.4	0	0	0	0	18	51.4	11	31.4	4	11.4	2	5.7	0	0
Standard Diet and B 4 - (first week)	21	1	7.9	31	88.6	2	5.7	2	5.7	0	0	0	0	11	31.4	17	48.5	1	2.8	4	11.4	2	5.7
Standard Diet and B 4 - (second week)	20	2	7.6	32	91.4	1	2.8	1	2.8	1	2.8	0	0	15	42.8	13	37.1	2	5.7	4	11.4	1	2.8

Table No. III - Conclusions derived from Table No. II. See key for symbols as in Table II.

Formula I but the number of soft feces showed an increase, the number where hard exceeded soft showed a decrease and the number where soft exceeded hard showed an increase. Again, these findings were more marked in the second week than in the first. When Formula II was used, there was a marked increase in the number of hard feces, a decrease in the number of soft feces, an increase in the number where hard exceeded soft and a decrease where soft exceeded hard. Once more, the findings were more marked in the second week as compared with the first. The findings for Formula IV were similar to those of Formula II but to a lesser degree.

From these experimental findings, we draw the conclusion that Formula I (Gelusil) is not constipating and that Formulae II and IV appear to be constipating. As Formla IV is identical with Formula I in its Aluminum Hydroxide content, both using the nonreactive type but Formula IV has magnesium trisilicate omitted, we conclude that nonreactive aluminum hydroxide without magnesium trisilicate is slightly constipating but less so than reactive aluminum hydroxide with magnesium trisilicate added and that a combination of nonreactive aluminum hydroxide with magnesium trisilicate (Gelusil) is not constipating at all.

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Preparation And Nutritive Value Of An Incomplete Acid Hydrolysate Of Casein

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IT HAS BEEN established by numerous investigators that nitrogen balance in the dog as well as in man can be maintained on a diet containing, as the sole source of nitrogen, an amino acid mixture produced by the acid hydrolysis of protein, provided tryptophane has been incorporated in adequate amounts. Obviously the cardinal requirement for nitrogen balance is that the nitrogen intake in the diet must contain adequate quantities of all the indispensable amino acids. With the exception of tryptophane, all indispensable amino acids are found and have been isolated from the mixture obtained by acid hydrolysis of protein. However, there are three debatable questions: (1) Does racemization of amino acids by hydrolysis of a protein occur in such amounts as to reduce the biological utilization of the resulting mixture? (2) Does the catalytic action of acids on proteins at boiling or at elevated temperature destroy partially or *in toto* any indispensable amino acid or unknown factor other than tryptophane? (3) Do any appreciable losses of essential amino acids occur during the removal of insoluble inorganic salts and subsequent purification of the hydrolysate?

In a preceding paper, Kade et al (1) have shown that dogs can be maintained in positive balance when fed 140 mg. of nitrogen per kg. of body weight as casein. The same quantity of a partial acid hydrolysate of casein supplemented with tryptophane is required to maintain positive nitrogen balance. Also, the data show that if an adequate amount of methionine is given, along with the casein, positive balance can be achieved with the feeding of only 90 mg. of nitrogen per kg. of body weight. Moreover, if the hydrolysate is fortified with methionine, the quantity of nitrogen necessary for equilibrium is reduced to 90 mg. of nitrogen per kg. of body weight. This is considerably less than the amount of nitrogen necessary as the native casein but approximately the same as the quantity required in the form of casein supplemented with methionine.

Elsewhere it was shown (Kade et al) (2) that a complete acid hydrolysate of casein supplemented with tryptophane will maintain positive nitrogen balance when given at a level of approximately 200 mg of nitrogen per kg. of body weight. Nitrogen equilibrium was obtained either by oral or intravenous feeding. This level of nitrogen administration is considerably greater than the minimum level of casein. Evidently the hydrolysate prepared according to the previous re-

port (2) is much less efficient than the native casein or the partial acid hydrolysate reported in the later paper. This decrease in biological efficiency necessitated an investigation of the method of its preparation.

Herein are presented: (1) a method for the preparation of a partial acid hydrolysate of casein, (2) evidence as to the non-antigenicity of this hydrolysate, (3) rat growth experiments, (4) the determination of the minimum nitrogen intake necessary to maintain equilibrium in dogs, and (5) intravenous nitrogen balance experiments in dogs.

Hydrolysis: For the preparation of protein hydrolysates suitable for parenteral injection, sulfuric acid has a decided advantage over other catalytic agents since sulfate ions can be removed almost completely as the insoluble barium salt. It has been common practice to use high concentrations of acid, in the neighborhood of 33 per cent, for the digestion of protein. The use of such concentrations is not necessary since it has been found that the amount of acid required for hydrolysis can be reduced to as low as 0.75 normal sulfuric acid, provided suitable conditions prevail and the concentration of protein is lowered from about 25 per cent to 5 or 6 per cent. The optimum concentrations of acid and of proteins as well as the time required for hydrolysis have been investigated. White et al (3, 4) have indicated that complete hydrolysis of protein is not necessary for the production of preparations satisfactory for parenteral administration. It has therefore been considered desirable to determine the relationship between the degree of hydrolysis, based on the ratio of alpha-

Table 1

Relation of Degree of Hydrolysis of Casein by 0.75-1.0 N Sulfuric Acid to Antigenicity in Guinea Pigs and Skin Reactions in Dogs
The degree of hydrolysis is expressed in terms of ratio of alpha-amino nitrogen to total nitrogen.

Preparation	Ratio of Alpha-Amino N to Total N	Antigenicity
1	48.0	++ +
2	49.4	++
3*	54.3	+ +
4*	59.6	+
5*	60.4	+
		—
6**	61.4	—
7**	61.5	—
8**	66.6	—

*With Preparations 3, 4 and 5 observations were made on skin reactions in dogs following repeated intravenous administration of sterile solutions. No antigenicity was observed in guinea pigs.

**With Preparations 6, 7 and 8 no antigenicity in guinea pigs or skin reactions in dogs were noted.

amino nitrogen to total nitrogen, and anaphylactic reactions.

This is of importance for the successful preparation of hydrolysates that can be parenterally administered repeatedly with safety. In Table 1 data are presented showing the relationship between these ratios and allergic manifestations. In testing such material the hydrolysates were first sterilized and tested for pyrogenicity.

It is apparent from the data presented in Table 1 that the hydrolysate of casein made in this manner should have a ratio of alpha-amino nitrogen to total nitrogen of at least 60. Preparations of lower ratios may contain molecules sufficiently large to produce undesirable side actions on injection. It has been noted that if intimate mixing of acid and protein is made prior to autoclaving, and internal temperature and pressure are raised to 121 degrees C. and 15 pounds respectively, a slightly higher ratio can be attained with 0.75 normal acid.

Purification: Following hydrolysis, major losses usually occur in the process of recovery and purification of the hydrolysate. The steps involved are: (1) Decolorization by active carbon; and (2) removal of sulfate by barium.

If the removal of coloring matter is performed by the addition of 2.5 to 3 per cent of activated carbon (Norit A) while the mixture is hot, losses of amino acids can be reduced to a minimum of about 5 per cent. Greater losses occur during the removal of sulfate by barium and subsequent filtration. For the purpose of recovery of a non-pyrogenic hydrolysate, it is desirable to expedite the rate of filtration and limit the washing of the precipitate so as not to dilute the filtrate; otherwise it would be necessary to distill the excess of water. By careful manipulation, the barium sulfate is removed by filtration at a temperature of 75 to 80 degrees C. The yield of a large number of batches by this process has repeatedly been found to be 80 to 85 per cent of the total nitrogen.

OUTLINE OF PROCEDURE

In the present process the concentration of casein is about 6 per cent and sulfuric acid, 0.75 normal. Digestion at an internal pressure of 15 pounds and a temperature of 121 degrees C. is maintained for 16 consecutive hours. The time for hydrolysis as recorded represents the actual hours which elapse after internal temperature and pressure reach 121 degrees C. and 15 pounds, respectively. The purpose of such a low concentration of acid and of protein is to reduce the amount of undesirable insoluble matter that must be removed and hence obtain a higher yield of amino acids.

The volume of filtrate is adjusted so that each cc. will contain 7.2 mg. of nitrogen (approximately 54 mg. of amino acids). to each cc. is added 1 mg. of nitrogen (6 mg of amino acids) as a mixture, comprised of 12 per cent *dl*-tryptophane, 15 per cent *dl*-methionine, and 73 per cent glycine. The resulting solution contains approximately 60 grams of amino acids per liter (8.2 mg. N) of which 1.2 per cent will be added *dl*-trypto-

phane, 1.5 per cent added *dl*-methionine, and 7.3 per cent added glycine. The alpha-amino nitrogen as determined by the formol method is 5.3 to 5.5 mg. and the ratio of alpha-amino nitrogen to total nitrogen is near 65 per cent. The amino acid mixture is immediately sterilized and stored in sterile containers until it is ready for use.

Antigenicity: The product prepared as described above was tested for its antigenicity as outlined below:

Guinea pigs weighing between 200 and 250 grams each were used. Since casein has been used as the only source of protein, half the number of animals in this test were sensitized to casein and the other half to the hydrolysate. Thus, 12 guinea pigs were given 3 cc. of 1 per cent sterile casein and 12 were given 3 cc. of the hydrolysate subcutaneously every day for five days. A three-week period was allowed to elapse at the end of which six of the animals sensitized to casein were given casein intracardiacally and the other six were given the hydrolysate. Six of the animals sensitized to the hydrolysate were given casein and the other six, the hydrolysate. Since only those guinea pigs sensitized to casein and shocked with casein exhibited any antigenic reactions, our present amino acid hydrolysate, prepared according to the method described, is non-antigenic.

RAT GROWTH

Animals: A Sprague Dawley strain of white rats raised in our colony was used throughout the investigation. The age was approximately 22 days at the start of this study.

Amino-acid mixture: The product described, which consists of a 6 per cent solution, was brought to dryness and used as the only source of protein nitrogen.

Diet other than amino acids: The food ingredients and the vitamin content of the diet are found in Table 2.

Table 2

DIET 39

Dried 6% Hydrolysate	22.00 gm.
Sucrose	67.86 gm.
Salt Mixture*	4.00 gm.
Methyl Cellulose	2.00 gm.
Vitamins**	0.50 gm.
Liver Extract	0.60 gm.
Halibut Liver Oil	0.04 gm.
Corn Oil	3.00 gm.
Alpha-Tocopherol	0.005 gm.
	100.005 gm.

* Jones and Foster (5).

** Vitamins per kilogram of food

Thiamine HCl	4.0 mg.
Riboflavin	8.0 mg.
Pyridoxine HCl	4.0 mg.
Nicotinic Acid	4.0 mg.
(d)—Ca Pantothenate	20.0 mg
p-Aminobenzoic Acid	600.0 mg.
i-Inositol	2.0 gm.
Choline HCl	2.0 gm.

Procedure: Each animal was kept in a clean, individual cage, under constant conditions of temperature and humidity. The rats were given food and water *ad libitum*. Food consumption and weight gain were recorded twice weekly. Growth was measured on this diet for 28 days. The results are found in Table 3.

Table 3

RAT GROWTH EXPERIMENTS

Sole source of nitrogen in the diet consists of 22% spray-dried acid hydrolysate of casein fortified with *dl*-tryptophane, *dl*-methionine and glycine.

Rat		Diet No. 154	
No.	Sex	Initial weight gms.	Gain in weight at 28 days gms.
1650	M	54	61
1654	M	51	88
1655	M	50	98
1656	M	48	95
1657	M	53	81
1658	M	49	106
1661	M	39	63
1662	M	41	76
1665	M	57	74
1669	M	39	75
1670	M	39	63
Average gain for 28 days (gms.) 71 per rat			
1641	F	41	70
1642	F	47	73
1643	F	42	88
1644	F	42	84
1645	F	47	58
1646	F	48	65
1647	F	47	71
1648	F	48	73
1651	F	49	50
1659	F	46	82
1660	F	47	84
1666	F	54	57
1668	F	58	63

Average gain for 28 days (gms.) 71 per rat

M = Male; F = Female

CONCLUSIONS

It is evident from the data presented that the amino acid hydrolysate contains at least all the indispensable amino acids known, and that these amino acids used as the only source of nitrogen in the diet of rats permit growth.

Litter mates grown on a diet wherein the sole source of amino acids was casein at a level of 22 per cent, grew more rapidly with an average gain in weight of nearly 5 gmt./day over the 28-day period. Since at this intake sufficient sulfur-containing amino acids are furnished to the rat, further supplementation by methionine does not increase the rate of growth. Whether this decreased rate of growth is due to the destruction of some factor necessary for rapid weight gain of the rat, or whether the processing has reduced the concentration of one of the essential amino acids below the optimum level for the rat, is being investigated.

MAINTENANCE OF NITROGEN BALANCE
IN DOGS

General procedure: The nitrogen balance studies were carried out by the procedure previously reported (2). The hydrolysate was administered as practically the sole source of nitrogen. It was given either orally by stomach tube or parenterally. The remaining dietary constituents were fed orally.

Experiment 1. Dog No. 16—weight 10.5 kg. This experiment was conducted to find the minimum level of nitrogen intake of the new hydrolysate which is required to maintain the dog in nitrogen balance. At the beginning of the experiment a level of 130 mg. of nitrogen per kg. of body weight was administered orally. During the second week the amount of hydrolysate was reduced to 110 mg. of nitrogen per kg. of body weight. The animal remained in positive nitrogen balance. The third week the intake was lowered to 100 mg. of nitrogen per kg. of body weight. At this level, more nitrogen was excreted than taken in. The nitrogen intake during the fourth week was raised to 120 mg. of nitrogen per kg. of body weight with a return to positive balance. The data are presented in Figure 1. It is evident from this experiment that dogs can be maintained in positive nitrogen balance on an intake of 110 mg. of nitrogen per kg. of body weight of the 6 per cent hydrolysate as the sole source of nitrogen.

Experiment 2. Dog No. 17—weight 8.5 kg. This experiment is similar to Experiment 1 on another animal. The first week a nitrogen intake of 110 mg. per kg. of body weight was administered orally, effecting positive balance. From the eighth to the fourteenth day 100 mg. of nitrogen per kg. of body weight was given. During this period the animal excreted 220 mg. more of nitrogen than was fed. From the fifteenth to the twenty-first day the nitrogen intake was 90 mg. per kg. of body weight. This resulted in a greater negative balance. From the twenty-second to the twenty-eighth day 110 mg. of nitrogen per kg. of body weight was administered. This was sufficient nitrogen to allow the animal to retain 878 mg. of nitrogen. The data for this experiment are presented in Figure 2. The results indicate that nitrogen balance can be maintained at a nitrogen intake of 110 mg. of the 6 per cent hydrolysate per kg. of body weight. When a lower level of 100 mg. or 90 mg. per kg. of body weight was administered, the dog was in negative nitrogen balance.

It was previously reported (1) that the dog requires less than 100 mg. of nitrogen per kg. of body weight in the form of a casein hydrolysate similarly prepared when supplemented with sufficient methionine and tryptophane for this species. Thus the limiting amino acid for the utilization of this preparation in the dog is either tryptophane or methionine. The optimum requirements of the dog for these two amino acids is under investigation. It is interesting to note that at the maintenance level of feeding, the dogs are receiving approximately 9.7 mg. of *dl*-tryptophane per kg. of body weight.

Experiment 3. Dog No. 17—weight 8.5 kg. In this experiment the dog was kept on the 6 per cent hydrolysate as the sole source of nitrogen. For the first seven days the amino acid hydrolysate was administered orally at a level of 140 mg. of nitrogen per kg. of body weight. For the second and third weeks the same quantity of the amino acid mixture was given intravenously. The fourth week the same amount was fed orally. The results of this experiment are presented

NITROGEN BALANCE PROTEIN HYDROLYSATE 6% SOLE SOURCE OF NITROGEN

DOG NO. 16 10.5 KILO
NITROGEN INTAKE:
DAYS 1-7 1365 MG. PER DAY 130 MG. PER KILO BODY WEIGHT
8-14 1155 " " " 110 " " " " "
15-21 1050 " " " 100 " " " " "
22-28 1260 " " " 120 " " " " "

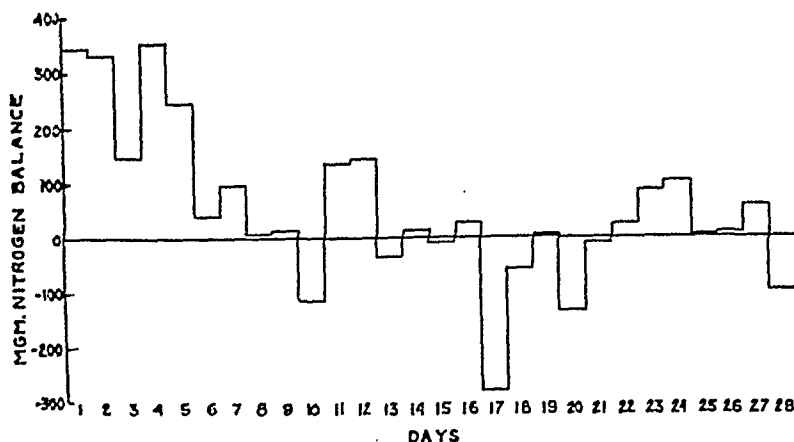


Fig. 1

in Figure 3. One hundred forty milligrams of nitrogen per kilogram of body weight, using a 6 per cent amino

experiment again the amino acid hydrolysate was administered to this dog orally, intravenously and orally

NITROGEN BALANCE PROTEIN HYDROLYSATE 6% SOLE SOURCE OF NITROGEN

DOG NO. 17 8.5 KILO
NITROGEN INTAKE:
DAYS 1-7 935 MG. PER DAY 110 MG. PER KILO BODY WEIGHT
8-14 850 " " " 100 " " " " "
15-21 765 " " " 90 " " " " "
22-28 935 " " " 110 " " " " "

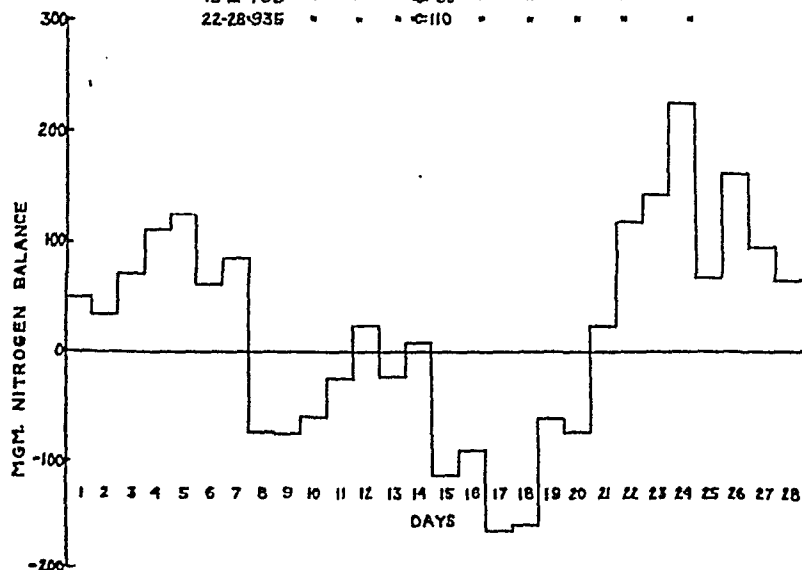


Fig. 2

acid hydrolysate as the sole source of nitrogen in the diet, maintains positive nitrogen balance by both oral and intravenous administration.

Experiment 4. Dog No. 16—weight 10.5 kg. In this

for four weeks. The nitrogen intake was 130 mg. per kg. of body weight. The data are presented in Figure 4. Irrespective of the method of administration, 130 mg. of nitrogen per kg. of body weight maintains this dog in positive nitrogen balance.

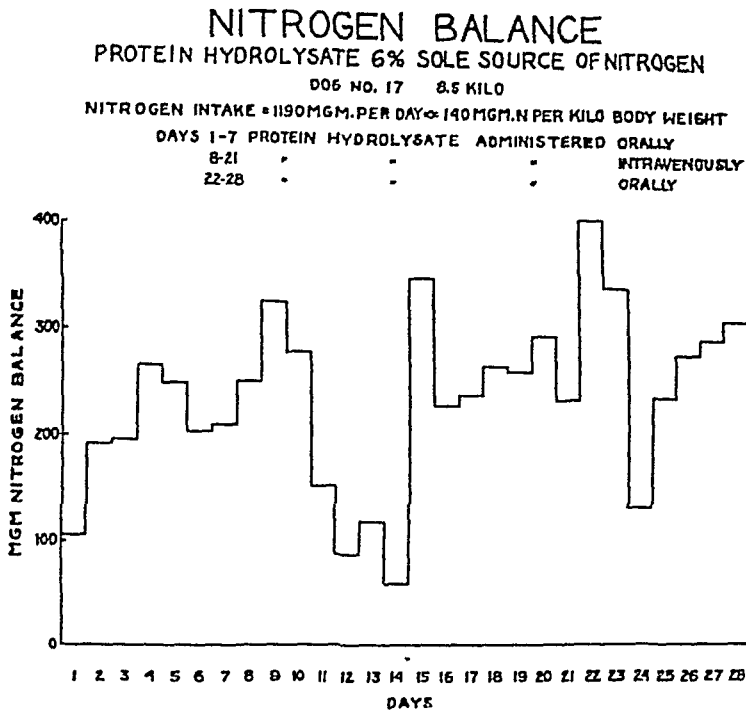


Fig. 3

SUMMARY

A method for the preparation of an incomplete acid hydrolysate of casein has been described. Pure amino acids are added to the hydrolysate so that the resulting

guinea pigs and has been shown to be non-antigenic.

Rat growth tests show that as the only source of nitrogen in the diet, the product is capable of promoting

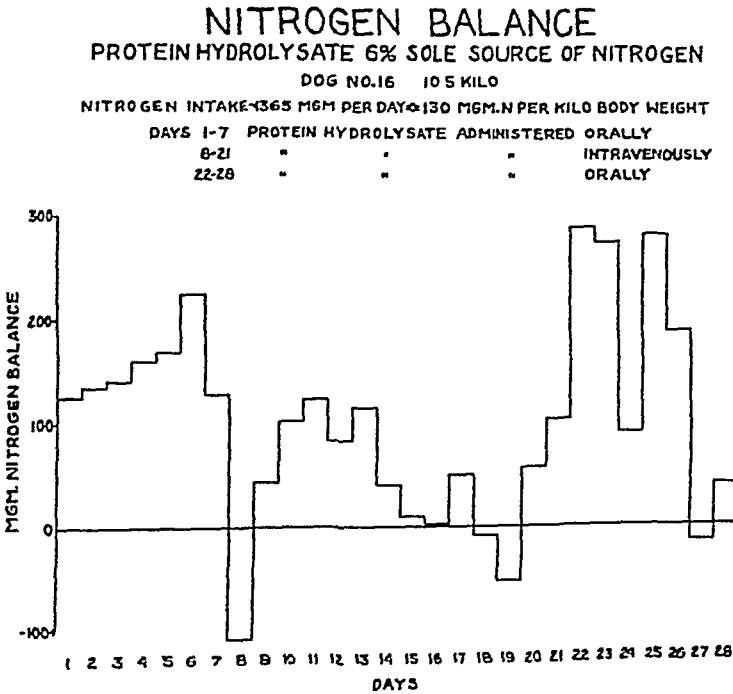


Fig. 4

mixture contains 1.2 per cent added *dl*-tryptophane, 1.5 per cent added *dl*-methionine and 7.3 per cent added glycine on the basis of total solids.

This preparation has been tested for antigenicity in

satisfactory growth.

The biological efficiency of this product has been tested in dogs and evidence has been presented to show that as the sole source of nitrogen in the diet, it is

capable of maintaining nitrogen balance at a level of 110 mg. of nitrogen per kg. of body weight by oral feeding. The hydrolysate will also maintain positive

nitrogen balance when administered intravenously.

The authors are greatly indebted to Benjamin Sahagian, William Phillips, Jessy Shepherd and Dolores Marcinkiewicz for technical assistance.

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Some Considerations on the Possible Relationship of Cholesterol Metabolism To Peptic Ulcer

By

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THERE ARE few conditions which have called forth as many therapeutic approaches as has peptic ulcer. While this, in itself, may be an index to the inadequacy of our present therapy, it can nevertheless be pointed out that we have been able to treat peptic ulcer with reasonable success for many years, primarily through the use of the Sippy Diet and alkalies. Thus it has been apparent for a long time that therapeutic success in peptic ulcer must rest upon neutralization and reduction of gastric acidity and that our major failure up to now has been due to the fact that we have been unable to devise a method by which gastric acidity may be maintained at a low level for prolonged periods of time. It is obvious, of course, that the Sippy Diet and alkalies can be effective for only brief periods of each day, and that the attempt to prolong such periods by continuous intragastric aluminum hydroxide drip is hardly satisfactory in a condition as chronic as peptic ulcer.

In more recent years such operative procedures as subtotal gastrectomy and transthoracic vagotomy, acting either by complete removal of the acid-bearing cells or by interruption of the nervous secretory mechanism, have succeeded in accomplishing what medical measures have thus far failed to accomplish; and the success of these operative procedures has, in itself, furnished further evidence that our therapeutic endeavors must lie in the direction of a prolonged reduction in gastric acidity. There is therefore the question as to whether or not we can accomplish a similar reduction in gastric acidity for lengthy periods of time by medical measures.

It has been known for some years that fat and its derivatives, fatty acids and soaps, have an inhibitory action on the gastric secretion and motility; that they

reduce the quantity and acidity of the juice with particular depression of the peptic power; and that they exert this effect while in the stomach and also after reaching the duodenum. According to Roberts (1) the less saturated the constituent fatty acids, the more efficient is the inhibitory power of the fat. Even more significantly, Lima (2) has shown that preparations of the blood itself (after the ingestion of oil) produce an effective inhibition of gastric motility. Moreover, there is considerable evidence in the literature and in clinical experience to indicate that conditions accompanied by a high blood fat and blood cholesterol are associated with a reduced gastric secretion and acidity, and either a reduction in the incidence of peptic ulcer or a beneficial effect upon a pre-existing peptic ulcer. While it is apparent that there are considerable variations for each individual in the rate of gastric secretion and in the HCL conduct of the gastric juice—and that these variations are dependent to some extent upon the cephalic, gastric, and intestinal phases and, in turn, are influenced by such factors as emotional and endocrine changes and the type of food ingested—it is conceivable that these variations may be carried on at a higher or lower level depending on the level of blood cholesterol and blood lipids. Cholesterol, a monatomic, unsaturated alcohol, while chemically unrelated to the blood lipids, appears to be physiologically related to them because of its constant occurrence along with fat and phospholipid. Various authors (3) have shown that hypercholesterolemia is invariably associated with sufficient increase in neutral fats and in other lipids of the blood to cause a marked lipemia. Cholesterol, itself exists in the blood plasma in two forms: free and as esters with fatty acids, with the ratio ordinarily 40% free to 60% combined; and, in the opinion of Sperry (4) the percentage of free to combined cholesterol (in the absence of severe

parenchymatous disease of the liver) is a physiological constant. Indeed, one of the primary functions ascribed to cholesterol in the blood plasma has been the transportation of fatty acids and it may not be too far-fetched to compare the relationship of cholesterol to fatty acids in the blood plasma to that of the relationship of hemoglobin to oxygen in the red blood cell. At any rate, I should like to point out at this time the evidence which appears to substantiate the intimacy of blood cholesterol (and blood lipids) with gastric secretion and peptic ulcer.

1. It has been recognized for some time that peptic ulcer is of rare occurrence in pregnancy, and that the peptic ulcers of women have a tendency to show remissions during pregnancy. Sandweiss et al (5) for example, found only one case of peptic ulcer in over 70,000 pregnant women. It is significant that numerous investigators (6) have shown a reduced gastric secretion and a hypercholesterolemia beginning in the second month of pregnancy and persisting until delivery.

2. Peptic ulcer rarely occurs in association with diabetes. Thus Rothenberg and Teicher (7) found that the incidence of peptic ulcer in all of their hospital admissions was 1.49% as compared with an incidence of 0.25% in their diabetes patients. Other investigators (8, 9, 18) have shown a reduction in gastric acidity in diabetes, and the hypercholesterolemia (17) which accompanies it has been recognized for many years.

3. The considerably greater incidence of peptic ulcer in males than in females (9) has been a subject of endless speculation, and it may be meaningful with respect to this fact that there is a higher average blood cholesterol in women than in men. According to Bloor (10) the lipids in the plasma in grams per hundred cc. are: for men; cholesterol, 0.22; total lipids, 0.67; and for women; cholesterol, 0.24; total lipids, 0.69. Moreover, it appears, through the work of Gildea (11) et al that these differences in blood cholesterol levels between the sexes may be even more marked in the presence of inanition. According to their findings, the stocky, heavy male showed a blood cholesterol concentration averaging 230 mg. per cent, while the slender, aesthetic type averaged only 168 mg. per cent; in women, these differences were not so clear-cut, the average cholesterol being 205 mg. per cent and 196 mg per cent in the two types. Similarly, in relation to the differences in gastric acidity between the sexes, VanZant (12) has shown that the modal free acidity for men ranges between 45-50 units in the ages of twenty years to forty, whereas the mode for women is approximately 35 units throughout adult life.

4. The decrease in the incidence of peptic ulcer after the age of 50 may likewise be explained, in part, by the increase in blood cholesterol and the decrease in gastric secretion with advancing years. Thus Hurxthal and Simpson (13) found a gradual increase in blood cholesterol with advancing age and Bloomfield (14) showed that the average values for total acidity at the age of 20-40, 40-60, and over 60 are: 54, 46, and 34.

5. The tendency for the symptoms of peptic ulcer to show remissions during the summer months may be

significant in view of Currie's (15) findings that the average blood cholesterol in normal people is much higher during that season of the year. And McEachern (16) in a study of seasonal variations in blood cholesterol, found that the highest levels were reached from the month of May to the month of July. (It may be worth while to point out in this connection that the foods which are most abundant in the Sippy Diet; namely, milk, cream, butter, and eggs, are richest in cholesterol content during the corresponding months).

6. Certain conditions generally accompanied by hypercholesterolemia such as: chronic cholecystitis, cirrhosis of the liver, and chronic nephritis (17) are apparently accompanied also by a greater incidence of hypochlorhydria and achlorhydria (18, 9). Obviously, abnormal blood cholesterol levels can be only part of the reason for altered gastric-acidity since certain conditions are associated with endocrine dysfunctions which may, in themselves, play a role in gastric physiology. For instance, in hyperthyroidism, which is generally accompanied by a lowered blood cholesterol, most studies have revealed the existence of hypochlorhydria and it is possible to explain this by the known association of the thyroid gland with the sympathetic nervous system and the inhibitory effect of the latter upon gastric secretion.

7. Finally, it may be worth while to point out that the effectiveness of the Sippy Diet may be due as much to the fact that it is richer in cholesterol content than the average diet as to its blandness or the frequency of its feedings.

It is apparent that the entire question of the relation of cholesterol and lipid metabolism to gastric secretion and acidity, and thus to the possible incidence and therapy of peptic ulcer—in view of the known inhibitory action of fat—has been woefully neglected. While it is true that a great deal of work in this respect has been done through the use of enterogastrone and urogastrone in recent years, it is my impression that the relationship between blood cholesterol and gastric acidity may be even more direct than these studies have implied. (Incidentally, though enterogastrone and urogastrone have been shown to be effective in the inhibition of gastric secretion, the same criticism as for other forms of medical therapy—an inability to maintain a reduction in gastric secretion for prolonged periods of time—may be leveled against them. And while it is obvious that hyperlipemia and hypercholesterolemia may inhibit gastric secretion to some extent through the release of enterogastrone, it must nevertheless be recognized that such action may thus be maintained for lengthy intervals.)

It has been known for some time that insulin (presumably through vagus stimulation) causes an increase in gastric secretion, and numerous other investigators have shown that it likewise causes a fall in blood cholesterol. Of equal significance are the findings of Cornell (19) which demonstrated that the total cholesterol falls from 10% to 30% within ten to thirty minutes after the injection of histamine. There seems almost certainly, therefore, an inverse relationship be-

tween blood cholesterol and gastric secretion and it is my impression that an alteration in one will provoke, in the absence of other factors, an alteration in the other.

Just one more thought along these lines: there has been a tendency to ascribe the hypersecretion induced by insulin to its stimulating action on the vagal centers, but it appears that the level of plasma cholesterol, perhaps through direct action on the parietal cells, may be equally involved. For one thing, it is apparent that blood glucose and blood cholesterol are intimately associated, and that a rise or decline in one is almost always associated with a proportionate rise or decline in the other. And for another, it is my opinion that Remesow (20) by demonstrating that (1) colloidal cholesterol and cholesterol esters are dialysable through a semi-permeable membrane, (2) the optimum dialysis takes place at a Ph of 7.8; and (3) the presence of glucose extends the range of optimum dialysis from Ph 3.5 to 11.5 and increases the rate of dialysis, has proven a more intimate relationship between cholesterol and glucose with respect to gastric acidity than had hitherto been supposed. The final explanations for the alterations in gastric secretion—perhaps even for an alteration in gastric mucosal resistance—provoked by fluctuations in cholesterol and glucose blood levels may thus lie in the direction suggested by Remesow.

If the inhibitory action of fat and fatty acids upon gastric motility, secretion and acidity may be utilized by increasing their level in the blood plasma through a primary increase in blood cholesterol, there still remains the question of how this may be accomplished therapeutically. There has been considerable controversy for many years over the subject of whether or not the blood cholesterol may be raised by dietary means, and it is only comparatively recently that it has been shown that it can be accomplished. The studies of Gardner and Gainsborough (21) demonstrated that the blood cholesterol can be raised and maintained on a high level through the prolonged feeding of a diet rich in cholesterol and that the rise in blood cholesterol is due to a relatively equal increase in the free and combined cholesterol. Their finding, however, though confirmed by some (22) have not been confirmed by all succeeding investigators—possibly because of a difference in methods. In more recent years, several investigations have revealed that the ingestion of lecithin, rather than cholesterol, is most effective in and responsible for the elevation of blood cholesterol. Thus Corwin (23) using dogs, found that lecithin alone, or lecithin added to a diet high in fat, will produce a marked hypercholesterolemia in which the rise is due to a proportionately equal increase in the cholesterol esters and free cholesterol.

And Steiner and Domanski (24) working with ten

patients of whom eight had rheumatoid arthritis and two chronic nephritis without edema, achieved an increase in serum cholesterol in two to eight weeks of from 40 to 218 mg. per cent through the daily addition of 100 grams of egg yolk powder (containing 14.4% lecithin and 8% cholesterol) to an otherwise normal diet. The level of serum cholesterol returned to normal in approximately a month after the discontinuation of the egg yolk powder. It is interesting that they obtained their results with subjects in all of whom the control blood cholesterol was in the high normal. Because of their own studies and the previous work of Corwin, they concluded that the lecithin (possibly through the lipotropic action of its contained choline, which has been shown to prevent the deposition of cholesterol in the liver) was chiefly instrumental in producing the hypercholesterolemia.

The way may thus be open, through an elevation in blood cholesterol by methods such as those employed by Steiner and Domanski, to evoke a more prolonged reduction in gastric secretion and acidity than has hitherto been accomplished by other medical measures. It is my opinion, certainly, that there is sufficient confirmatory evidence in such a direction to warrant further investigation into the entire subject. There may, of course, be argument—on the basis of a possible involvement of cholesterol in the production of arteriosclerosis—against the deliberate raising of its level in the blood plasma. But I know of no incontrovertible studies which indicate that a high blood cholesterol is either the primary or secondary cause of arteriosclerosis. The arteriosclerosis of diabetes, for example, has been shown to occur without relationship to the level of blood cholesterol (25). Hirsch and Weinhouse (26) concluded from a review of the subject that most cases of arteriosclerosis unassociated with diabetes or hypothyroidism do not show hypercholesterolemia, and that the disease may develop without hyperlipemia. And since there is isolated evidence to indicate that cases of peptic ulcer, just as cases of inanition (27, 11) are accompanied by a lowered blood cholesterol, I can see no contraindication to a procedure which would raise it to normal or high normal levels.

SUMMARY

1. Evidence has been cited from clinical and experimental observations to show that gastric acidity, secretion, and motility may be influenced by the level of blood cholesterol.

2. The suggestion is made that peptic ulcer may thus be treated by a prolonged elevation in blood cholesterol through the addition, in the form of egg yolk powder, of relatively large amounts of lecithin and cholesterol to the diet.

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Epidemiology Of A Food Poisoning Epidemic (Staphylococcus Enterotoxin)

By

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IT WAS BELIEVED worthwhile to report the case findings and treatment of an epidemic of food poisoning due to staphylococcus enterotoxin because of its magnitude and severity, thorough investigative procedure and source of infection.

Three meals were served at the Detachment in the usual manner on 16 September 1946. A menu of the meals follows:

Breakfast

Chilled Tomato Juice	Fried Bacon
Fresh Milk	Apple Jam
Assorted Dry Cereals	Coffee
Scrambled Eggs	Fresh Cantaloupes

Dinner

Baked Spare Ribs	Sliced Fresh Tomatoes
Candied Yams and Mashed Potatoes	Apple Cobbler
Spanish Sauce	Hot Rolls
Buttered Corn	Raw Vegetable Salad
*Chicken Salad	Coffee — Iced tea with lemon

Supper

Baked Franks	Boiled Issue Beans with Bacon
Scalloped Potatoes	Apple Sauce Cake
Buttered Spinach	Left-over Ribs
Raw Vegetable Salad	Bread — Butter — Coffee

The offending food appeared to be the chicken salad at the noon meal. This was based on the following facts:

1. Incubation Period: — Dined at 1135 and first case became ill at 1500 with peak at 1930 the same day.
2. Chicken salad with mayonnaise was ingested by all sick cases.
3. The clinical picture in these cases was that of typical staphylococcus enterotoxin poisoning.
4. Pork spare ribs were ingested by some men but all the hospital admissions ate the chicken salad. In addition, the brief incubation period and clinical

course ruled out trichinosis as a potential etiologic factor. There were no protracted periods of convalescence, eosinophilia or residua of trichinosis. Salmonella organisms were not recovered from any of the affected cases and agglutination tests were negative. The clinical course and agglutination tests excluded acute brucellosis as a possibility. The clinical picture did not resemble botulism.

Preparation of Chicken Salad: Chicken: The chickens were delivered to the mess on 13 September 1946. They were frozen and appeared to be in good condition. They were thawed out in the morning of 14 September 1946, cleaned, and refrigerated again. They were removed the morning of 15 September 1946, and were fried for the noon meal of 15 September 1946. There were extra fresh chickens which were prepared on the morning of 16 September 1946 for chicken salad. This was intended as an additional dish.

The residual chickens were boiled the morning of 16 September 1946, and the stock was removed. Chicken was cooled for 30 minutes and cold water added so the chicken could be handled. The flesh was separated from the bones, chopped finely, peas added with left-over breakfast eggs, salt and pepper, and mayonnaise. After boiling, the chicken, was exposed for 90 minutes, and replaced in the icebox where remained for 1 3/4 hours. It was removed just prior to serving. In all, about 10 gallons were served to 700 men.

Mayonnaise: Freshly opened, one-gallon jars of Bestyett Brand were used. One and one-half gallons were employed. The remaining half-gallon was taken to the laboratory for study.

Men employed in preparation of chicken salad: two attendants were the only men who actually handled the chicken salad prior to ingestion. The men served themselves at mealtime.

Bacteriology Studies:

Culture Media Employed:

Blood agar, eosin-methylene blue, Kliger's, shigella-

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agar, desoxycholate, bismuth sulfite agar, carbohydrate broth media, anaerobic media, and plain agar.

A. Meat and Mayonnaise cultures — no growth.

B. Finger lesion culture of mess attendant revealed pure growth of *Staph. albus*.

C. Feces cultures (of seriously ill cases).

Lab. No.: 135 — *Staph. albus*, *Strep. hemolyticus*, *B. Coli* group.

136 — *Staph. albus*, *B. Coli* group, anaerobic staph. and strep.

137 — *Staph. albus*, *B. Coli* group, anaerobic staph. and strep.

140 — *B. Coli* group and *B. proteus*, anaerobic staph. and strep.

D. Throat Cultures (of 4 cases of U. R. I.) among kitchen staff.

Lab. No.: 1 — *Staph. albus*, *Strep. hemolyticus*.

2 — *Neisseria*, Diphtheroids.

3 — *Neisseria*, *Staph. albus*.

4 — *Neisseria*, *Micrococcus tetragenes*.

Attention has been called in the past to several large outbreaks in the United States apparently caused by either white or yellow staphylococci (1). There were no *Shigella* and *Salmonella* types identified. *Clostridium botulinum* was not present.

CONCLUSION

The lesion from the fingers of one mess attendant revealed a pure culture of *staph. albus*. Stool cultures in three out of four cultures revealed *staph. albus*. Throat cultures revealed *staph. albus* in two out of four cases. The mayonnaise and meat cultures gave no growth. There was no chicken salad available for culture as it had been completely used the day before and inserts cleaned. Virulence tests were not available.

Condition of the Mess on 17 September 1946: The floors, walls, and cooking utensils appeared clean. Garbage disposal was adequate and efficient. Mess hall inspection W2 made daily by a detachment officer. The last medical inspection was made 26 August 1946.

Physical Examination of Entire Mess Staff:

Colds — Three cases.

Pharyngitis — One case.

Acne Vulgaris — One case.

These men were not connected with direct manufacture of offending food and did not handle inserts or pots.

Probable source of infection: The probable source of infection was a mess attendant who had a ringworm infection of the right forefinger with marked pitting of nail and left small finger for two months. The latter became infected and cracked open, 13 September 1946. He treated it himself with "some medicine". This finger was bandaged when he came to work and, of course, it became soaked after handling the chickens. At the time, there was involvement of the nailbed resembling a low-grade chronic paronychia. There was also

an excoriated crusted area at the finger tip. He was taken back to the hospital for more adequate bacteriologic specimens.

Apparently the chicken salad was not chilled throughout in the four large inserts, allowing staphylococci to incubate and multiply with the elaboration of the offending enterotoxin. It must be assumed that the affected soldiers partook of the inadequately refrigerated center portion of the food contained in the large inserts. The probable source of infection was the kitchen worker with an infected finger.

Susceptibility to the Enterotoxin: There may be a lack of susceptibility in some individuals but there are, unfortunately, many sources of error involved ordinarily in obtaining such information. Some attacks may be so mild as not to be reported; the food involved may not contain enterotoxin at the time of food distribution but may develop it later under suitable conditions of time and temperature; portions of food in large bulk may come from an improperly refrigerated centre; and the dosage of enterotoxin may vary with the amount ingested. In a collection of epidemics reported by six observers, Dack (2) quotes the susceptibility as ranging from 60 to 100 per cent. In our series it was only 5.4 per cent, since 43 patients were admitted out of a possible 790 men who ingested the offending food. This figure should have been higher since many had symptoms so mild that they did not seek treatment.

Clinical Study: A total of 43 cases of food poisoning were sufficiently ill to be admitted to the hospital. There was an undetermined number of milder cases that did not seek medical care. The attacks were characterized by cramping, abdominal pains associated with severe episodes of vomiting and diarrhea. They usually appeared with explosive suddenness. About seven cases showed signs of mild collapse and these were treated more intensively. Temperatures were taken but were not elevated appreciably. Most of the patients presented skeletal muscle cramps, probably due to loss of chlorides from excessive vomiting and a tendency toward alkalosis. Blood counts and urinalyses and agglutinations tests performed on the more serious cases were normal.

Treatment: In view of the sudden influx of a large number of patients requiring emergency treatment, they were divided into 3 groups according to severity: —

1. Mild: Bismuth and paregoric (dram 1 (4 cc.) hourly, till relieved); sedatives, tea with sugar, as desired.

2. Moderate: $\frac{1}{8}$ gr. (0.008 gm.) morphine sulfate, p. r. n.; bismuth and paregoric, drams 1 (4 cc.) every hour till relieved. Intravenous clyses of 5 per cent glucose in normal saline solution were employed when indicated.

3. Severe: $\frac{1}{4}$ gr. (0.008 gm.) morphine sulfate, p. r. n.; intravenous clyses of 5 per cent glucose in normal saline solution and plasma as indicated for signs of impending collapse.

After anorexia subsided, patients were placed on a liquid diet and then on soft diet. Hospital stays ranged from 12 to 72 hours for the more seriously ill patients. All the patients recovered from the attack and returned to full duty status.

SUMMARY

An epidemic of food poisoning due to *Staphylococcus*

enterotoxin elaborated in a chicken salad affected 43 men of a 790 man Detachment on 16 September 1946. The probable source of inoculation was traced to a finger infection in one of the two men directly engaged in its preparation. *Staphylococcus albus* was obtained on various culture media in pure growth. The mess officers and attendants were instructed in the future prevention of food contamination.

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Pruritus of the Perineum

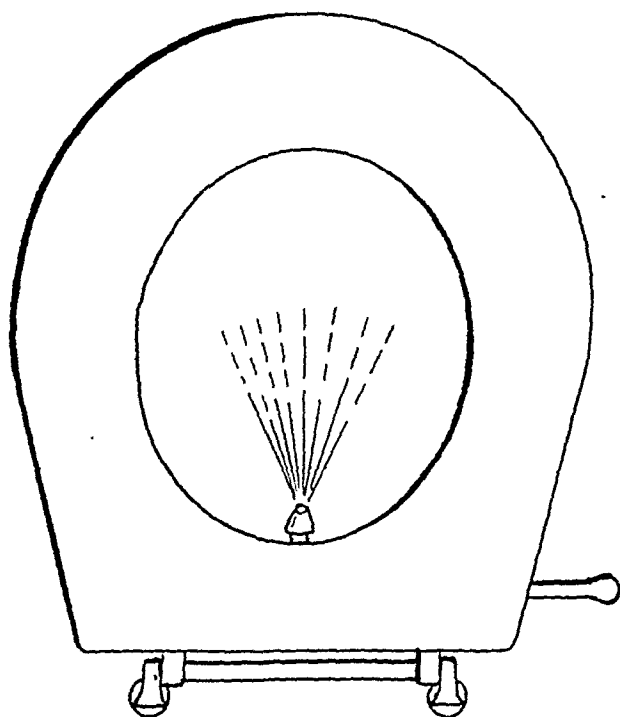
By

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THE STIMULUS for this paper emerged from a patient who concerned himself with the problem of hygiene of the perineum. He presented me with a picture of his contrivance and has requested my opinion. He wanted to know whether "itching of the anus", of which he heard a lot, is a condition that warrants the preventive approach he has visualized through the employment of his apparatus in combatting and obviating the ravages of this malady.

A survey of the literature revealed that the operative treatment of anal pruritus seemed to have come into prominence on the basis of structural pathology. The lesion resides either remote or at the site of symptomatology — the perineum; hence the classification: direct and indirect. The majority of cases fall in the former, while the latter center about the visceral source of the disease. Among the local factors in causation of pruritus, poor hygiene was not accorded due recognition. In a patient having a diseased gallbladder and anal pruritus, the latter may be both direct and indirect in etiology and perpetuity. It becomes abundantly apparent, that anal pruritus on the basis of inadequate cleansing has thus far not arrested the attention of the general practitioner, and the treatment directed is not usually from the simple to the complex. One wonders how many cases of this type of pruritus have been the subjects for aggressive type of therapy: irradiation, injection of alcohol and tattooing.

The contrivance referred to in the beginning of this article, in my opinion possesses features of preventive measures and, therefore merits a careful examination. The instrument was invented by a lay individual, Mr. Herman H. Sohn of Providence, R. I. and relates to



improvements in "Seats for Toilet." The purpose of his invention is to incorporate in the seat structure a spraying apparatus for discharging over the perineum "Suitable liquid" (I presume the inventor meant a solution with antibiotic quality) and to secure cleansing by manually operable means for discharging the antiseptic liquid forcibly.

The drawing above, labeled Figure 1 in the inventor's specifications, was chosen among others for its simplicity. "It is a plan view of a toilet seat with the spray apparatus embodied therein."

It seems to the writer that even physicians are apt to

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harbor a spurious sense of modesty and avoid interrogation about personal hygiene after defecation. The simplest cause of anal pruritus, *poor hygiene*, has not been given the prominence and importance in current literature, that has been accorded to the direct and indirect causes. The fact that pruritus is an accompanying factor in the causation of anal pruritus—a condition

which is preventable at first, and when neglected becomes irreversible. The dictum of Joslin-speaking of diabetes—"a washed neck does not boil", may well be applied to conditioning of the perineum. To render the perineum less susceptible to trauma resulting from scratching and to ensuing infection is a much desired addition to the treatment of a primary condition at its source.

Editorial

IS ULCERATIVE COLITIS A PSYCHOGENIC DISEASE?

The object of psychosomatic studies is not primarily to show that disease is psychogenic but to correlate emotional and mental manifestations with physical changes. The immediate task is to establish a "psychological profile" for groups suffering from the same physical diseases, so that on recognizing a characteristic profile, one may say,—"This individual psychologically suggests that he is the type who might develop angina pectoris or peptic ulcer or diabetes, and so on." The Dutch physician, J. Groen (1) claims to have found a very constant psychological picture in patients suffering from chronic ulcerative colitis and almost concludes that the disease is psychogenic. His paper is ably written and evidences careful investigation and reflection, his conclusion is tentative rather than final and his discussion serves to cushion the shock of his obvious belief in the psychogenesis of the disease. The case reports indicate that careful diagnosis was established in each of the six individuals and that the author was deliberate and objective in his assessment of their personality characteristics. He refers to his method of examination as *biographic anamnesis*, as contrasted with analysis, for it is merely a sympathetic and detailed inquiry into the antecedents of the patient, his interests, life history and problems. The persons studied appear to present a rather constant mental and emotional constellation—good intellect, carefulness, neatness (sometimes "sissyness"), decency, decorum, sensitiveness, self-depreciation, strong *narcissism*, egocentricity, limited ambition, lack of aggression, fearfulness, yearning for affection, domesticity, sentimentality, emotional immaturity, mother-fixation, adoption of mother surrogates, and restraint when speaking of their intimate thoughts. This portion of his paper agrees, in large part, with other psychological assessments of ulcerative colitis and also with one's memory of his own cases.

Groen seems to have discovered a coincidence in time in each of the cases between the appearance of a strong conflict and the beginning of intestinal symptoms. He was able always to put his finger on an emotional episode immediately preceding the outbreak of the colitis. This is an association suggesting a casual relationship and further search for such coincidence should be made by other investigators in larger series of cases before

concluding that this pattern always exists. He found that under the stress of love-loss, marked humiliation and frustration, the physical disease—ulcerative colitis—is likely to come on very quickly, out of a blue sky, manifesting itself by diarrhea with blood and pus. With similar speed the symptoms were found to subside once the emotional field was quieted by the removal of the stress, by reassurance and especially by a practical solution of the individual's dilemma. Without special study of cases with this point in mind it would be ill-advised for anyone to express his natural disinclination to accept the author's belief. Much depends upon the investigator's objectivity of interpretation. What Groen describes seems parallel to the onset of coronary thrombosis. Writing of his heart affliction, Dunbar (2) states—"The coronary accident in these patients is precipitated by an apparently irreparable mutilation of their picture of themselves through external threats to their authoritative role." In peptic ulcer, again, it now seems certain that the lesion develops as a result of increased nervous tension transmitted via the vagus nerves. The history in acute peptic ulcer frequently indicates that the first serious symptom of gastric pain coincided with some kind of emotional stress, and x-ray studies undertaken at once may show extreme spasm of the stomach and duodenum, sufficient to suggest "pseudo-ulcer". Groen found that the symptoms of colitis persist so long as the patient's anxiety continues and then rapidly ameliorate and disappear once the cause of anxiety has been removed by a change in the life situation. Theoretically, his suggestion that ulcerative colitis is psychogenic derives considerable support from what we accept today with respect to the causation of peptic ulcer. He disarms bold criticism of his thesis by stating—"Most physicians will probably remain skeptical as yet about the possibility of the psychogenesis of ulcerative colitis." He is not unqualifiedly dogmatic and desires that much more work be done on this point. It is true that his thesis will be received with very great skepticism by pathologists who have examined the tissues of the bowel in *chronic thromboulcerative colitis* and by clinicians who have observed protracted cases with sepsis, and with the serious dermatologic, ocular and joint manifestations which seem to be a part of the syndrome.

In a person of sensitive temperament harboring a dormant intestinal infection, a sudden psychological

stress might be expected to favor a precipitation of active inflammation. Most peoples' lives are filled with frustrations and acute problems yet the incidence of ulcerative colitis is not great. This is not a valid criticism, however, on Gröen's own terms of a special kind of personality necessary to the manifestation.

A bilateral transthoracic vagotomy might do no harm

on some chronic case, who would consent to help us find out if this disease actually comes from the brain.

BEAUMONT S. CORNELL

1. Groen, J.: Psychogenesis and psychotherapy of ulcerative colitis. *Psychosomatic Medicine* (May-June, 1947) IX, 3, 151-174.
2. *Psychosomatic Diagnosis* by Flanders Dunbar (p. 336) Paul B. Hoeber, Inc., New York, 1946.

Book Reviews

Proceedings of the Eleventh Annual Convention of the National Gastroenterological Association. Pp. 187, (\$2.50), Medical Authors Publishing Co., New York.

Following an introduction by Dr. Samuel Weiss, the papers given at the Association meeting in June, 1946, are presented with discussions. Four symposiums on the following subjects—peptic ulcer, infectious hepatitis, psychosomatic medicine and gall bladder disease take in a wide range of interest.

Gastritis. By Rudolph Schindler, M. D., pp. 462, (\$10.00). Grune and Stratton, New York, 1947.

The author devotes considerable space to clarifying definitions used in connection with descriptions of the various forms of gastritis. His introductory chapters indicate that gastritis, as an accepted entity, did not exist until after the first world war and the introduction of the gastroscopic technique. Broussais (1831) gave a vast impetus to gastritis by coming to what the author calls an "intuitive conclusion", although his anatomic observations were ill-founded. Since then the profession has periodically accepted and rejected gastritis as an entity. The value of Schindler's work, not only

his extended researches in gastroscopy and histopathology, but the present book as well, lies in the fact that no one can survey his work without believing that gastritis has come to stay. He divides chronic gastritis into (1) idiopathic chronic gastritis and (2) chronic gastritis associated with other gastric pathology. In the treatment of chronic idiopathic gastritis discontinuance of tobacco is urgent, but wines are permitted in atrophic gastritis. Treatment includes eradication of infective foci and cure of deficiency states. Reticulogen is recommended in atrophic arthritis. Gastric lavages have lost some of their popularity, but still represent a valuable means of direct medication. Diet schedules are given in detail. Although Schindler has come out with a book whose objectivity is obtrusive and unequalled for its value, he demonstrates his wide experience and erudition by revealing frankly his psychosomatic tendencies in placing psychotherapy at the top of the list in treatment. This is a beautifully illustrated, substantial text which will at once take its place among the valuable and enduring monographs in gastroenterology.

Abstracts

CLINICAL MEDICINE

MOUTH AND ESOPHAGUS

Patterson, C. O.: *Medical management of esophageal disorders.* (Texas Med. J., May 1947, XLIII, I, 9-11).

For malignant stricture of the esophagus in inoperable cases, the author places a radium capsule in the stricture and follows this up by adequate dilatations, having two patients alive and well after 5 years. He describes esophageal obstructions in pemphigus, in scleroderma and in epidermolysis bullosa in which careful dilatations produced virtual cures. In each case, the obstruction was due to a specific lesion of the disease.

STOMACH

Blegen, H. M. and Kintner, A. R.: *Aggravation of a*

gastric ulcer following dorsolumbar sympathectomy. (J. A. M. A., April 19, 1947, 133, 16, 1207-1208).

The authors describe a case of gastric ulcer who, following a sympathectomy for hypertension, experienced post-operatively 3 serious hemorrhages from the ulcer, the ulcer being successfully treated later by partial gastrectomy. Reference is made to a similar case recently reported by Weeks, Ryan and Van Hoy (J. A. M. A. 132: 988-990 (Dec. 21) 1946), of a case of duodenal ulcer and hypertension whose ulcer symptoms improved following complete transthoracic vagotomy and removal of the left thoracolumbar sympathetic chain, but who developed perforation of the ulcer with fatal peritonitis soon after the second stage sympathectomy was done. It appears that while vagotomy favors the healing of peptic ulcer, sympathectomy exerts an adverse effect.

MONAT, H. A.: *Modern gastroscopy: observations.* (Rev. Gastroenterology, May 1947, 14, 5, 320-324).

The author offers many practical suggestions for doing a gastroscopy—a knowledge of the patient, proper use of local anesthetics, method of introducing the instrument, etc., and stresses the fact that the operator is not in a position correctly to interpret his findings until he has done several hundred examinations.

BOWEL

CEDERMARK, J.: *Tumtarmsneurinom.* (Nordisk Medicin 16. 34, April 18, 1947, 944-946).

Neurinoma of the Small Intestine

After a brief review of the literature, the author reports the five cases of primary tumor in the small intestine operated upon at the surgical department of the Karolinska Hospital since 1940. Two of them were carcinomas. The other 3 were neurinomas, 2 malignant and one benign. The main symptom in the latter cases was intermittent melena with anemia, provoked by necrosis in the tumor and perforation into the intestine. The first case was first operated on under the diagnosis of ulcer and later for too hasty gastric evacuation. Not until 13 years later, when a palpable tumor developed, was the correct diagnosis revealed at operation. The tumor, a neurinoma, which had then become malignant and metastasized, was removed as much as possible. The patient died six months later from a recurrence. The second case ran a similar course in five years. The third case, in which anemia was diagnosed eight years earlier, was thought to be an inoperable pancreatic tumor on exploratory laparotomy at another hospital. On later operation at the Karolinska Hospital the tumor was found to be a benign retroperitoneal neurinoma in the duodenum.

The author assumes that neurinoma in the small intestine is more common than appears from the literature and points out the advisability of keeping this possibility in mind in cases of obscure melena. Exploratory laparotomy is suggested for such cases. Neurinomas of the small intestine may cause severe clinical symptoms even before becoming malignant. The prognosis should be favorable if operation is done in good time.

FRIEDMAN, SYDNEY M.: *Pattern types in the small intestines.* Am. J. Roentgen. & Radium Therapy. 57, 1, 36. January, 1947.

The normal pattern of the duodenum, although subject to fairly wide variation, shows certain definite characteristics in its roentgenographic features. In the first stage there are longitudinal folds during contraction which disappear as the cap fills. In that part of the second stage which is above the ampulla, there is in most instances, an absence of folds. The ampulla itself is usually discernible as a small round negative shadow. Transverse folds, broken in the middle, appear at the ampulla or a little above and increase in size and con-

tinuity through the remainder of the second stage. Thickening of the folds and an increase in their number gives the third stage an appearance intermediate between that of the duodenum and the fine reticulated or feathery appearance of the jejunum.

The first variation was the presence of transverse folds in the first stage of the duodenum. The second variation consisted of a duodenum dilated as far as the ampulla, notches of contraction were present in the adjacent wall. The third type was that of a uniformly large lumen, which did not alter in size. A pattern in which the barium did not outline the folds but rather was disposed in globular masses was considered the fourth type. A uniformly small lumen was noticed as the fifth type. Coarse or thick rugae giving a ro o ro or scroll-like pattern were noted as type six.

In the jejunum and ileum the author saw the following types: (1) excessively thick rugae in the upper part of the small bowel. (2) Heavy irregular folds. (3) "Snow-flake" pattern. (4) Spastic small bowel as seen in hypoproteinemia in dogs.

Franz J. Lust.

SANDERS, R. L.: *Management of carcinoma of the colon.* Texas Med. J., May 1947, XLIII, 1, 17-21).

This paper is a strong plea for one-stage operations where they can be performed. Since 1939 with improved anesthetics and better pre-operative rehabilitation, the mortality rate of the operations has been reduced from 33.3 per cent to 1.5 per cent. Improvement in technique has made it possible for the surgeon to approach each case more boldly and with better hope of good results.

COLE, W. H.: *Carcinoma of the colon.* (Illinois Med. J., May 1947, 91, 5, 229-238.

Constipation and rectal bleeding are among the early symptoms of colonic cancer and pain also occurs early, as a cramp-like sensation, in roughly 80 per cent of cases. Anorexia and nausea may occur early. Vomiting usually signifies obstruction. Weakness and anemia are late manifestations. Cancers in the right side of the colon are more palpable and carry a more severe anemia than those on the left side. Diagnosis is assisted by sigmoidoscopy and x-ray. Anemia, hypoproteinemia, and malnutrition must be corrected before resection is performed. The chief cause of peritonitis is not soilage, but leakage. Complete obstruction usually requires immediate colostomy with resection later. Loop colostomy is preferable to tube colostomy. Since the introduction of sulfasuxidine and sulfathalidine, open anastomosis may be considered safe, but such drugs are not substitutes for sound surgery.

HARGREAVES, E. R.: *Epidemic diarrhea and vomiting.* (Brit. Med. J., May 24, 1947, 720-722).

Two outbreaks of diarrhea and vomiting occurring at two county institutions in Cornwall during 1946 are described. These outbreaks were part of a widespread

epidemic among the surrounding population. With the exception of three deaths, all in aged patients, symptoms were mild and conformed to previous epidemics reported in the literature, a summary of which is included. Evidence obtained from these Cornish outbreaks points to an air-borne disease with an incubation period of 72 hours, the portal of entry being either the upper respiratory or the gastro-intestinal tract; the organism is probably a virus. The relation between epidemic diarrhea and vomiting in adults and that which occurs in newborn babies is discussed; the evidence points to the two conditions having a separate aetiology.

PANCREAS

JOHANNESON, C. J.: *Extensive calcification of pancreas*. (Northwestern Med., 46, 4, 286, April 1947).

The author presents a case of diffuse calculi within the head, body and tail of the pancreas in a man of 41, who in the army showed sugar in the urine, which cleared up on dietary treatment. His complaint was pain in the epigastric region coming on two hours after eating, with formation of gas. The author recommends high abdominal scout films in cases where unexplained densities are noted in the course of a gastro-intestinal x-ray series. Until recently only 18 cases of diffuse calcification of the pancreas had been reported.

LIVER AND GALL BLADDER

SNELL, A. M.: *The management of jaundiced patients*. (J. A. M. A., April 19, 1947, 133, 16, 1175-1180).

Success in the management of jaundiced patients depends on increased accuracy of diagnosis, especially in the differentiation of obstructive from hepatocellular jaundice. The author discusses "profile" hepatic functional studies, especially those concerned with urobilinogen metabolism. Indications for surgical intervention in cases of jaundice include (1) the proved or presumed presence of stone, (2) the development of jaundice after cholecystectomy, (3) the presence of associated biliary fistulas and (4) proved complete acholia. Serious primary or secondary hepatocellular injuries are contraindications for surgery. The established principals of medical treatment include a highly nutritious diet, the maintenance of normal hemoglobin and protein levels, the use of vitamins for the correction of specific deficiencies and the use of lipotropic substances and liver extract.

WILENSKY, A. O.: *The pathogenetic nature of the hepatic cirrhoses*. (Rev. Gastroenterology, May 1947, 14, 5, 331-339).

The author attempts to demonstrate the difference between the forms of cirrhosis of the liver. The essential nature of the *Laennec* form of cirrhosis is a slowly developing chronic lymphangitis in the interlobular stroma of the liver, with later contraction of the fibrotic scar tissue. The intimate interior structure of the hepatic lobule is not affected in this disease except

as a consequence of the contracting fibrotic tissue, so the reticulo-endothelial system remains intact. The *Hanot* type of hypertrophic cirrhosis is essentially a systemic disease of the reticulo-endothelial system of a group of organs including the liver, spleen, pancreas and associated lymph nodes. The process is really a destruction—a reticulo-endotheliolysis—of the elements of the reticulo-endothelial system in these organs.

THERAPEUTICS

BUSCHKE, F. AND CANTRELL, S. T.: *Supervoltage roentgen therapy of carcinoma of the esophagus*. (J. A. M. A., May 10, 1947, 134, 2, 127-129).

Although results have shown no definite cures, a technique has been worked out which has thus far given promise of ultimate success in some cases, e. g., seven-year and two-year cures. Probably with 200 kilovolt radiation therapy in about half of the cases of cancer of the esophagus which are still in a sufficiently good general condition to support the procedure, temporary reopening of the obstruction lasting from six to eighteen months can be expected. A proportion of these growths are radiovulnerable and require at least 5000 roentgens in a period of about forty days for complete sterilization. It is best to use only an anterior and posterior port. Preliminary gastrectomy should be avoided.

SURGERY

BACON, H. E., LINDE, S. A., AND MURRAY, F. H.: *Surgical treatment of lesions of the lower bowel*. (Rev. Gastroenterology, May 1947, 14, 5, 305-311).

The authors prefer "proctosigmoidectomy" in malignant lesions of the anus, rectum and sigmoid colon, because of low mortality, decreased morbidity, satisfactory survival rate and preservation of sphincter function. D. J. Hamilton in discussing the paper said, that considering the difficulties of Bacon's operation, its successful results could only be attributed to the operator's unusual personal skill.

AGUSTSSON, H., TUDOR, R. B. AND CHISHOLM, T. C.: *Hypoglycemia associated with hyperplasia of the Islets of Langerhans: report of a case successfully treated by surgery*. (Journal-Lancet, May 1947, LXVII, 5, 190-192).

A case of an infant 4 months old is reported in which 65 per cent of the pancreas was removed because of hyperinsulinism. Pathological report showed microscopically an increase in the number of the islets of Langerhans, some of which were hypertrophied. The "spells" which led to the ultimate diagnosis were characterized by a sudden cry while at rest and unconsciousness before the mother could reach the crib, followed by stupor for the next 24 hours. Only two other cases in which pancreatic resection for hypoglycemia in infants was done, have been recorded. Recovery was prompt and the follow-up showed an apparently normal infant. Early diagnosis in these cases is imperative to prevent cerebral damage.

Sugar Tolerance Tests --- Methods and Evaluation*

By

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THE SUGAR TOLERANCE TEST is a very important diagnostic procedure particularly in the person who has glycosuria. In the patient who is found to have marked glycosuria and a considerably elevated sugar in a specimen of blood, the sugar tolerance test is not really necessary, because the diagnosis of diabetes is comparatively simple. On the contrary, in the case with a 1 plus sugar in the urine, the sugar tolerance test is of great value in determining the significance of the glycosuria.

It is of special value in recognizing cases with renal glycosuria because restriction of the carbohydrates has no appreciable effect on renal glycosuria and the use of insulin may produce hypoglycemia readily. Perhaps because of the loss of sugar in the urine, these individuals, particularly those underweight, should have increased carbohydrate in the diet. There are other instances in which the test is useful such as the case of pancreatic tumor with hypoglycemia and that with a questionable diagnosis of Addison's Disease in which hypoglycemia develops after oral or intravenous glucose.

TESTS FOR SUGAR TOLERANCE

What tests for sugar tolerance should one use? I believe at present it depends in a large measure on one's individual experience with a given test and one's ability to interpret it. However, this idea may need alteration since Mosenthal (1) has shown that the nonglucose reducing substances in the blood vary from 10 to as much as 80 mg. per cent in cases.

Since the nonglucose reducing substances have no bearing on the carbohydrate metabolism, a considerable error may be introduced in this way. The blood sugar method of choice is usually the Folin-Wu procedure which includes the nonglucose non fermentable reducing materials as sugar. It may be necessary eventually to use generally as the standard method one which estimates only the fermentable sugar, presumably glucose, in order to obtain a proper knowledge of the true blood sugar.

Although sugar tolerance tests are used widely, the interpretation of them varies greatly. Some investigators interpret the sugar tolerance according to the peak of the blood sugar curve. Others interpret it according to the rate of the blood sugar fall and still others interpret the sugar tolerance according to the peak and the rate of fall. This last method of interpretation is probably the safest.

Glucose tolerance tests should be done under controlled conditions, otherwise, various factors may

cause a normal person to show a diabetic type of sugar tolerance. Certain variations in the diet may produce abnormalities in a sugar tolerance. Consequently, a patient should have been on an unrestricted diet for about three days prior to the test.

In the usual, practical work, the sugar tolerance test, if carefully done, is consistent enough to be of great value in the diagnosis of diabetes.

In the clean cut case, the diagnosis or the interpretation of the blood sugar curves is easy with any method. But, with any method of testing the glucose tolerance, or any other blood determinations, there are always the borderline results in which the interpretation of the test is questionable. Sometimes an additional test may be of value.

TYPES OF TESTS

In general, there are three types of glucose tolerance tests. One is the standard oral glucose tolerance test in which 100 Gm. of glucose is taken orally after an overnight fast and the blood sugar is determined one-half, one, two, and at times three hours after the ingestion of the glucose. The second is the Extton-Rose Method (2), in which the patients are given 50 Gm. of glucose after the fasting blood sugar has been determined. At the end of one-half hour a second blood sugar is taken and another 50 Gm. of glucose are given. When another half-hour has passed a third blood sample is obtained. In the case of the diabetic, the third blood sugar will be definitely higher than the second. In the case of the non-diabetic individual, the third blood sugar will be lower or only possibly slightly higher than the second. The third is the intravenous glucose tolerance, in which a given amount of glucose is injected intravenously and the blood sugar is determined at certain intervals after the injection of the sugar.

INTRAVENOUS GLUCOSE TOLERANCE TEST

Numerous investigators have experimented with the method, but considerable confusion has arisen from the results owing to the varying strengths and amounts of solution used and the varying time taken for injection of the glucose solution.

Two methods have been employed, namely: the continuous administration of a weak solution of dextrose for varying periods of time or the rapid injection of more concentrated solutions. The amount of glucose injected by various investigators has varied from 100 Gm. to as little as 3.5 Gm. Some give a standard total dose of the glucose, whereas others give it in terms of tenths grams per kilo of body weight. The concentration of the solution injected has varied from

* Address given to the Clinical Society of the New York Diabetic Association on May 16, 1947 at the New York Academy of Medicine, Edmund L. Shlevin, M.D., Chairman.

7 per cent to 50 per cent and the volume of the final amount of the fluid or solution injected has ranged from 20 cc. to as much as 500 cc. The time of injection has ranged from 20 seconds to 30 minutes, and in rare cases continuous injections.

Tunbridge and Allibone (3) have given an excellent presentation of this subject. Their procedure was to inject into the vein in three minutes, 92 cc. of a 30 per cent solution of dextrose dissolved in water; which represents 27.6 Gm. of dextrose. Blood samples were taken at intervals of one and one-half to seven and one-half minutes for at least 60 minutes after the end of the injection.

The maximum height to which the blood sugar rose varied somewhat with different subjects, but the blood taken one minute after the injection gave the maximum reading for the blood sugar. The usual value in the normal subject, one minute after the end of the injection was approximately 350 mg. per 100 cc. blood with a variation of 40 mg. above or below this point.

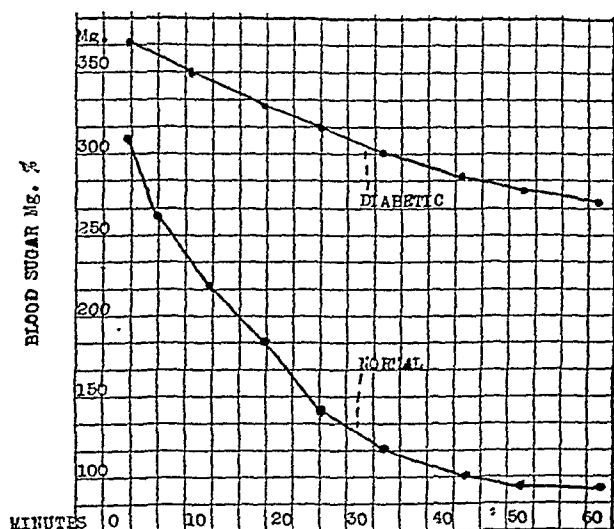


Chart 1.—Blood sugar curves following the intravenous injection in three minutes of 27.6 Gm. of glucose in a normal person and in a diabetic patient with a fasting blood sugar of 92 mg.

In this test, the blood sugar returned to the pre-injection level within 60 minutes in the healthy young person. The weight of the normal subjects in these tests varied from about 120 to 200 pounds and no specific effect could be signed to variations of weight within these limits.

In the normal person, glycosuria has been observed in the urines examined varying in amounts from .25 to 2.4 Gm.

In the cases of diabetics, the curves showed abnormal responses, in that the blood sugar level dropped comparatively little after the injection of the glucose.

There have been a number of complications following the intravenous administration of dextrose in the human subject. The chief complications reported have been pyrexia, rigors, general malaise, and headaches. In addition there has been pain in the arm and also phlebitis.

I would use the intravenous dextrose tolerance test for special research problems or in the case with disturbance in absorption in the gastrointestinal tract.

But for the general practical purposes I would recommend or use the standard oral glucose tolerance test.

STANDARD ORAL TEST

In my experience, I have used chiefly the standard oral glucose tolerance test, in which 100 Gm. of glucose is taken after an overnight fast, and the blood sugar is taken one-half, one, two, and three hours after the glucose ingestion. In children, I have used the dose of 50 Gm. of glucose for those who weighed less than 75 pounds and have given 75 Gm. for children who weighed more than 75 pounds. Various authors have stated that satisfactory tolerance curves for diagnostic purposes can be obtained with 50 Gm. of glucose as well as with 100 Gm., even in adults. This may be true to a large extent. But, in the normal person, the larger amount of sugar may prolong the hyperglycemia obtained, and in the diabetic both a higher level and a prolongation of the hyperglycemia may be produced.

CRITERIA

The criteria for interpreting the normal sugar tolerance are rather difficult to fix, because of the variable blood sugar curves which have been reported for the so-called non diabetic persons. A paper on the criteria for determining the normal sugar tolerance using 100 Gm. of glucose, was written by Gray in 1923, who studied 300 apparently healthy persons. His data showed the average normal fasting blood sugar to be 0.09 per cent and the average postprandial values to be 0.14 per cent in one-half hour, 0.12 per cent in one hour, 0.11 per cent in two hours, and 0.09 per cent in three hours. Others have reported higher values for normal sugar tolerance curves even with the maximum peak of about 0.18 per cent or more after the glucose ingestion. Joslin believes that the normal values usually do not exceed 0.14 per cent although the diagnosis would not be justifiable unless a value of 0.17 per cent was attained.

I would like to discuss first the results of sugar tolerance tests made in the course of studies and observations in glycosuria as found in 114,738 consecutive selectees, which were divided into two groups. In the first group of selectees, there were 45,650 persons (4). Of this group .8 per cent of the cases were found to have glycosuria and it was considered from the history of the selectees and from the blood sugar studies in the others that 57 per cent of those with glycosuria were diabetic or 47 per cent of this entire group of men were diabetic.

It was concluded that there must be many cases of unrecognized diabetes in the general population that could be diagnosed if routine urine tests were made on the general population, and if sugar was found, to do sugar tolerance tests when indicated. I wish to refer particularly to the second group of 69,088 selectees in whom the following studies (5) were made.

METHODS

All men had routine urinalyses. The final results of the qualitative amounts of sugar in the urine were

recorded according to Benedict's method as 1 plus to 4 plus.

Glycosuria varying in degree from 1 plus to 4 plus was found in 1,383 or 2.0 per cent of the 69,088 selectees examined. The qualitative amounts of sugar in the urine in the 1,383 cases were sugar 1 plus in 651 cases, 2 plus in 229 cases, 3 plus in 147 cases, and 4 plus in 356 cases.

In a group of 479 cases in which there was no verified history of diabetes, the men had sugar tolerance tests made on a subsequent day. A standard dose of 100 Gm. of dextrose was employed and ingested after an overnight fast. The concentration of the sugar in the blood and urine was determined in specimens taken during fasting and at intervals of one-half, 1, 2, and sometimes three hours after the ingestion of the dextrose. The determination of the blood sugar was made on 2 cc. samples of venous blood according to the method of Folin and Wu. In most instances, the tests were made in cases presenting sugar 1 plus in the urine which did or did not disappear in subsequent specimens of urine.

In this study, sugar tolerance tests were called normal if the fasting blood sugar level was below 130 mg. per hundred cubic centimeters and if the peak of the curve fell below 165 mg. per hundred cubic centimeters in one-half or one hour after the ingestion of the glucose and no sugar was found in the urine at this level. Potential diabetes was diagnosed when the subject had a blood sugar concentration of approximately 165 mg. per hundred cubic centimeters in one-half or one hour and some or all of the urine specimens contained sugar after the ingestion of the glucose. Diabetes was diagnosed when the blood sugar concentration exceeded a level of 170 mg. in one-half or one hour and some or all of the urine specimens contained sugar after the ingestion of the glucose, even though the fasting blood sugar was normal, 130 mg. or less, and the fasting urine was sugar free. No doubt some of these are borderline cases.

I think it is best and safer to consider persons with peaks in blood sugar curves of 165 mg. with sugar

in the urine as potentially diabetic even though there are no symptoms. Overlooking these cases would be much like overlooking cases of minimal tuberculosis found on routine x-ray examinations of the chest in persons without symptoms.

INCIDENCE OF DIABETES

The results of the analysis of the sugar tolerance tests made in 479 selectees with glycosuria showed that 190 persons had normal blood sugar tolerance curves, 38 were potentially diabetic and 251 (52 per cent) were diabetic according to Joslin's criteria, with peaks in blood sugar curves exceeding 170 mg. If the criteria of others should be used, these figures would vary. If a blood sugar level above 180 mg. is used as the lower diagnostic limit there would be 202 diabetics (42 per cent) and 87 potentially diabetic in this group of 479 cases. If, further, cases with normal fasting blood sugar and with maximum blood sugar of 180 to 200 mg. in which the two hour blood sugar was under 120 mg. were excluded, the diabetic group would be reduced to 158 cases (33 per cent), and the potential and borderline cases would be increased to 131 cases in this group of 479 cases.

NORMAL CURVES

With the available data of the 190 normal sugar tolerance curves it was possible to study 114 of these in relation to glycosuria during the tests. Of these 114 cases 69 showed no glycosuria during the sugar tolerance tests, whereas 45 showed sugar in some or all of the urine specimens during the tests, and the peak of the blood sugar curves was usually less than 140 or 150 mg. In the normal curves the fasting blood sugar was 65 to 130 mg.; the two hour blood sugar was 60 to 75 mg. in 34 cases, 80 to 115 mg. in 146 cases, and 120 to 140 mg. in 8 cases.

DIABETIC CURVES

In 212 of the 251 cases of diabetes the fasting blood sugar was normal and most of the fasting urine specimens were sugar free. The fasting blood was 80 to 130 mg. The peak of the blood sugar curve rose to

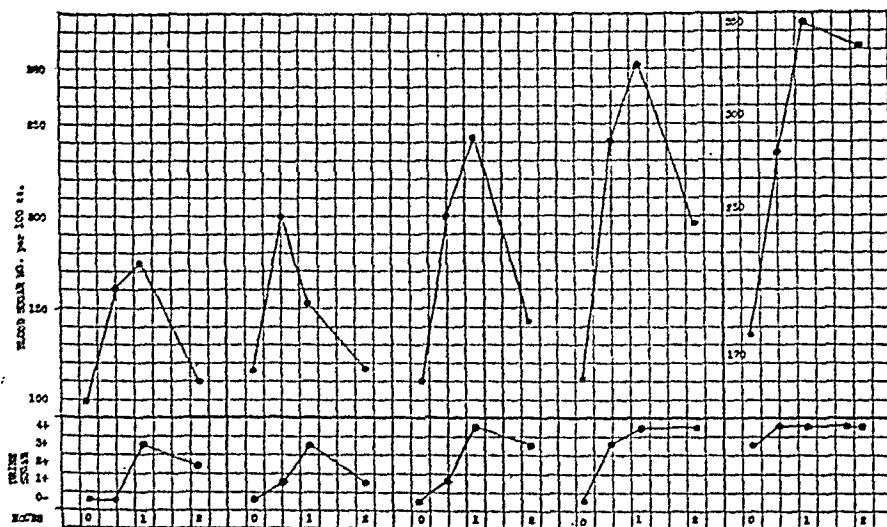


Chart 2.—Sugar tolerance after ingestion of 100 Gm. of glucose in selectees found to have diabetes.

levels above 170 mg. to as much as 385 mg. in one-half or one hour after the ingestion of glucose and some or all of the postprandial urine specimens contained sugar.

The two hour blood sugar levels ranged from 80 to 225 mg. If one would judge this group of diabetic patients by the fasting urine and blood sugar findings, a diagnosis of diabetes would not be made. Typical sugar tolerance curves of the diabetics are given in Charts 2 and 2a. The diagnosis of potential diabetes was made in 38 cases in which the peak of the sugar tolerance was 165 mg. There was a considerable

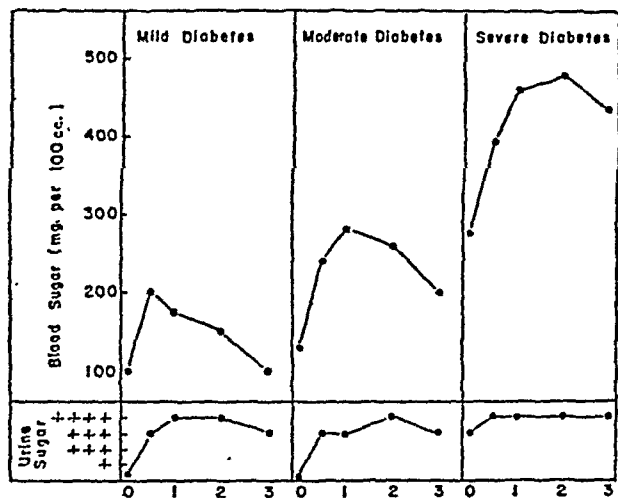


Chart 2-A, Characteristic Results in Mild, Moderate and Severe Diabetes Mellitus at Hourly Periods after the Ingestion of 100 Gm. of Glucose.

amount of sugar in the urine in these cases which is hard to explain on another basis. They should be classed, at least, as potential or incipient cases and treated as such until proved otherwise.

The degrees of glycosuria during the sugar tolerance tests usually ranged between 2 plus and 3 plus in all the diabetic and potential cases. There was an appreciable number with sugar 1 plus and comparatively few cases with sugar 4 plus in the urine during the tests.

There were only 39 cases in which the abnormal fasting blood sugar levels ranged from 135 to 365 mg. with fasting glycosuria. Of these, the maximum levels varied from 200 to 544 mg. per hundred cubic centimeters in one-half or one hour after the ingestion of the glucose, and the two hour blood sugar levels ranged from 120 to 500 mg. per hundred cubic centimeters.

The amount of glycosuria found on the routine examinations did not indicate always the severity of the diabetes because there were cases of urine sugar 1 plus giving blood sugar curves of moderately severe diabetes and cases of sugar 3 or 4 plus giving curves of mild diabetes.

FAMILY HISTORY AND NATIONALITY

There are several factors which should be taken into consideration in attempting to interpret some of the borderline sugar tolerance curves such as thyroid

disease, use of thyroid extract, infections, liver disease, family history, and nationality. Two of these which I wish to comment on particularly are the family history of diabetes and the nationality.

Certainly, if a person had a borderline sugar tolerance curve and he gave a strong family history of diabetes, no doubt this would cast more suspicion on this curve as being diabetic. It was found that 43.7 per cent of those who knew they had diabetes or glycosuria gave a family history of diabetes compared with 5.2 per cent of family histories of diabetes in the non diabetics.

In addition there are certain nationalities in whom the frequency of glycosuria and diabetes is much more common than others. There, too, in the borderline cases of sugar tolerance tests, the interpretation of the results would be somewhat affected by the nationality of the individual.

In the selectees it was of unusual interest to study the various individuals according to their nationality and the incidence of the glycosuria and diabetes. It has been proverbial that the Jews have the largest incidence of diabetes. This is not true here because their incidence in the diabetes group was the same as in the controls. It was found, for example, that the French-Canadians, the Irish, and the English had the highest incidence of glycosuria and diabetes. This is strongly illustrated in Table 1.

TABLE I

Incidence of Nationality in 332 Diabetics, of Whom 222 Were Newly Discovered

Nationality	332 Diabetic Per Cent of Cases	222 Newly Found Diabetic Per Cent of Cases	Control Group 7350 Selectees Per Cent of Cases
Canadian-French	18.4	17.1	9
Irish	22.3	24.3	11
Old American	13.3	14.0	45
Italian	6.9	7.2	10
English	11.5	11.3	5
Jewish	5.8	4.1	6
Portuguese	6.6	7.7	5
Other Nationalities	15.3	14.3	9

RENAL GLYCOSURIA

The sugar tolerance test is a most important asset in the diagnosis of renal glycosuria. In our first study (6) of glycosuria in selectees we found that 33 cases of renal glycosuria as determined by sugar tolerance test, occurred in 367 cases of Mellituria. Renal glycosuria has been regarded as a rare disease, but I feel that if more sugar tolerance tests were made, renal glycosuria would be found to be more frequent than has been in the past. Renal glycosuria is a benign condition in which there is an excretion of glucose in the urine, in the presence of a normal blood sugar. The renal threshold for sugar varies with individuals. Some restrict the diagnosis of renal glycosuria to conditions in which the renal threshold is extremely low, as indicated by the fact that all specimens of urine, even with a blood sugar of 70 mg., examined contain sugar. Others however, have slightly less strict criteria for this diagnosis and may use 80, 90, 100 mg. or more of blood sugar as the threshold for sugar.

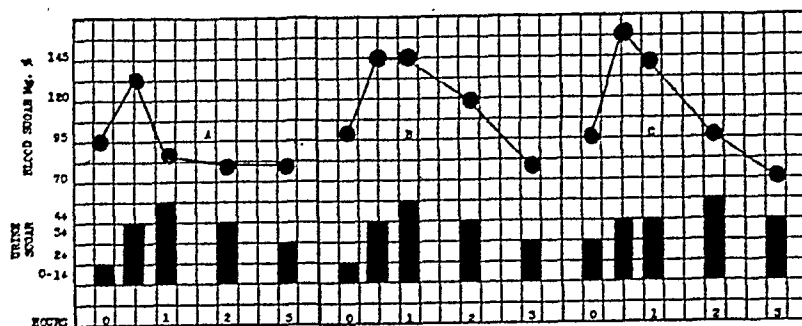


Chart 3.—Illustrations of sugar tolerance results obtained in renal diabetes following the ingestion of 100 Gm. of dextrose. A represents 13 cases, B 11 cases and C 9 cases.

Possibly our criteria were less strict than some of the others. However, it is important to recognize renal glycosuria, because diabetic treatment is unnecessary in these cases and it is possible that the restriction of carbohydrate may be even harmful, particularly in those thin, underweight persons with this condition.

Renal glycosuria appeared predominately in the younger persons as illustrated in Table 2.

TABLE II

Ages of Thirty-three Patients with Renal Glycosuria

Age, Years	Number of Cases
20-25	17
26-29	6
31-34	3
38-44	7

The average weight of these individuals was normal or sub normal except in two cases as shown in Table 3. There were no symptoms referable to this disease.

TABLE III

Status of Weight of Thirty-three Persons with Renal Glycosuria

Number of Cases	Weight According to Height & Age
12	7 to 14 pounds underweight
5	22 to 33 pounds underweight
14	Normal weight
2	43 to 64 pounds overweight

OTHER FACTORS INFLUENCING THE TOLERANCE CURVE

The sugar tolerance may be influenced by certain

other factors, such as previous diet. With normal individuals who have either been starved or kept on a low carbohydrate diet or a diet high in fat, a diabetic curve may be obtained after the ingestion of the dextrose. If the same individual is placed on a higher carbohydrate diet he will be found to have a normal tolerance curve at a later date.

Some advise that at least three days elapse before a test is done and that a diet with at least 250 grams of carbohydrate, eighty grams of protein, and calories sufficient for maintenance, be used. It has been noted that if doses of dextrose are given to normal individuals on successive days the rise of the blood sugar curve becomes less marked as the days go by; or if on the same day, successive doses of glucose are given the second curve reaches its peak at a lower level than the first and the third lower than the second, etc. A common explanation for these findings is that the carbohydrate stimulates the pancreas so as to produce more insulin.

PREVIOUS USE OF INSULIN

The previous use of insulin may cause a temporary loss of tolerance for carbohydrate. I (7) studied the sugar tolerance in a group of normal thin persons made to gain weight with insulin. The sugar tolerance tests were made before, during, and after the period with insulin treatment.

In a certain number of these people the curves for the blood sugar were normal either before or after the use of insulin, but during the period of treatment with insulin they had developed a considerable increase

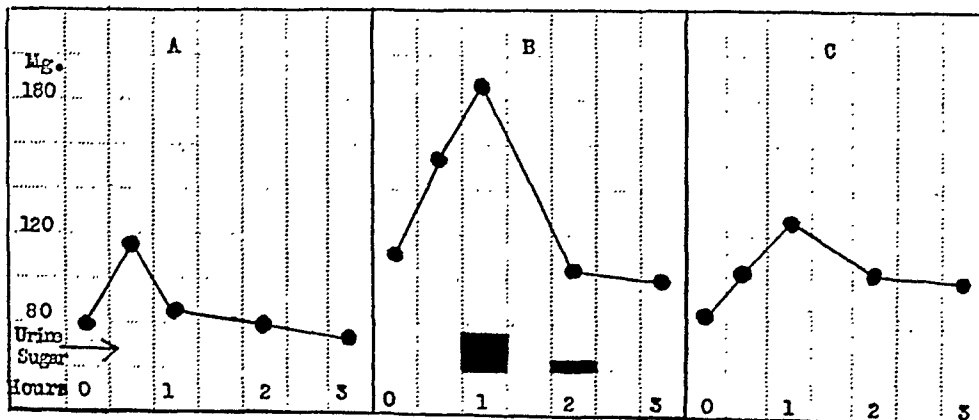


Chart 4 — Illustration of blood sugar curves resulting from the ingestion of 100 Gm. of glucose by 4 thin people; A, before; B, during and C, after insulin treatment. In B, .4 Gm. and .1 Gm. sugar were excreted in the urine one and two hours respectively after taking glucose.

in the concentration of the blood sugar in one-half or one hour after the ingestion of the dextrose and this was associated with glycosuria which usually appeared in one or two hours. This is shown in Chart 4.

The cause for this temporary decrease in tolerance may be due to a temporary suppression of the pancreatic function due to a rested pancreas or an inhibition of the normal islet secretion in compensation for the excessive amounts of insulin present following its injection.

PHYSICAL INACTIVITY

There have been a number of conditions which have been said to be a factor in diminishing sugar tolerance. Conditions such as age; diseases such as tuberculosis, hypertension, nephritis, arthritis, neurological diseases and blindness, etc.

There appears to me one factor that is common to most of these diseases, and that is physical inactivity or diminished activity. It has been recognized that exercise increases the utilization of dextrose. In contrast, there has been little or no work to show the effect of physical inactivity or effect of prolonged bed rest on the carbohydrate metabolism in non diabetic persons.

I (8) studied this problem by observing whether the carbohydrate metabolism was disturbed in a group of non diabetic patients who had been confined to bed for relatively long periods of time. There were seventy consecutive non diabetic patients whose weights were normal or slightly below normal and whose ages ranged from 18 to 92 years. The patients were on a routine house diet consisting of 250 Gm. of carbohydrate, 70 of protein, and 75 Gm. of fat. The patients had such diseases as tuberculosis, progressive muscular dystrophy, hemiplegia, multiple sclerosis, arthritis, hypertension, gout, cardiacs, Parkinson's Disease, amputation of both legs, fracture of hips or legs, etc. Practically all of these patients had been confined to bed for considerable periods of time before admittance to the hospital.

Before the sugar tolerance tests were made, the patients had been confined to bed in the hospital from one month to eight years. When the diminished sugar

tolerance tests were found in these adults, it was thought that age might be a factor. Consequently, a group of 16 children whose ages ranged from 4 to 14 years were studied also. Most of them were in casts or in traction. They had been confined to bed for periods ranging from 7 months to 14 years. They had such conditions as tuberculosis of the spine, coxavera, clubbed foot, old poliomyelitis, etc.

RESULTS IN ADULTS

In general, there is a diminished sugar tolerance in the patients who have been confined to bed for considerable periods of time. Of the seventy adults, 63 had definitely diminished sugar tolerance curves. Typical examples are shown in Chart 5. The fasting blood sugar ranged from 70 to 130 mg. in 100 cc. One hour after the ingestion of the dextrose the blood sugar rose to abnormal levels, the maximum being 364 mg. per cent.

In all of these cases, the specimens of fasting urine contained no sugar. After the ingestion of the glucose, considerable amounts of sugar varying from 1 to 4 plus were found in the urine. However, it was quite striking to find that frequently the urine was free from sugar, when simultaneous levels of the blood sugar were 200 or 250 mg. Apparently, there is a high renal threshold for sugar in these cases.

Of ten patients who have been confined to bed for long periods, the sugar tolerance tests were repeated after they had been ambulatory from two to six months. The blood sugar was found to be improved in some of these cases as illustrated in Chart 6.

RESULTS IN CHILDREN

The results of the sugar tolerance tests in sixteen inactive children were of unusual interest, because here too, the tolerance was diminished, particularly as compared with the results obtained in normally active children. However, the children's sugar tolerance curve did not rise as high as those of the adults. The examples of the sugar tolerance curves are given in Chart 7.

The fasting levels of the blood sugar of the children ranged from 90 to 107 mg. The greatest rise in the

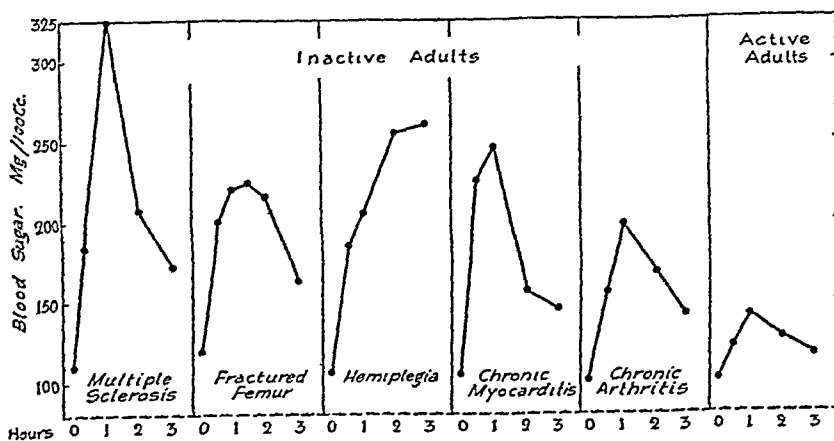


Chart 5.—Illustrations of blood sugar curves following the ingestion of 100 Gm. of dextrose for 63 nondiabetic adults with various diseases who had been confined to bed from one month to eight years.

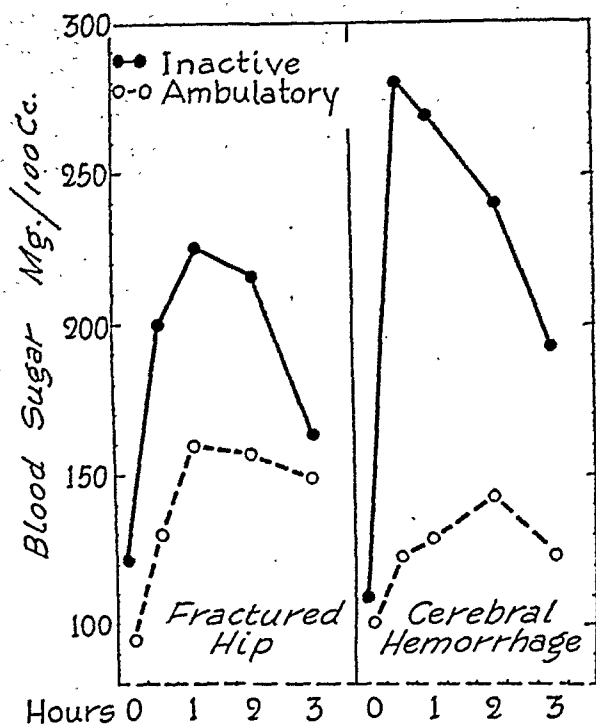


Chart 6.—Comparison of results of sugar tolerance tests of some patients when they were confined to bed and after they had been ambulatory for several months.

blood sugar one hour after the ingestion of the glucose was 238 mg.

The specimens of the fasting urine of the children showed no sugar. After the ingestion of the glucose some of the subjects had varying amounts of sugar in the urine. Some of the children seemed to have a diminished renal threshold for sugar, since sugar 1 plus and 2 plus was found in the urine when the blood sugar was at a level of from 115 to 167 mg.

ARTERIO VENOUS DIFFERENCE IN BLOOD SUGAR

It has been suggested that the lack of muscular utilization of sugar was the cause of the abnormal results obtained in these sugar tolerance tests. If this were the case, one would expect the physically in-

active patients to have diminished differences in the simultaneous values for the arterial and venous blood sugar.

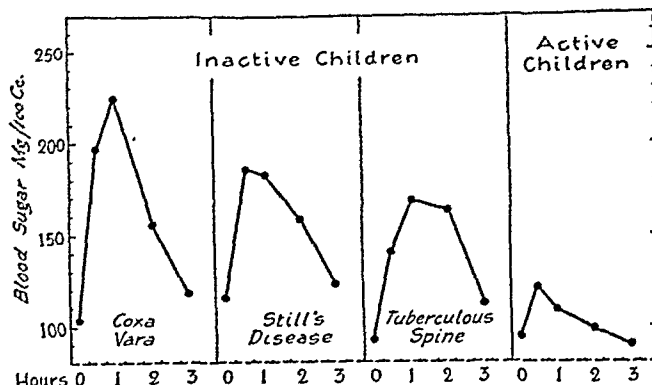


Chart 7 — Characteristic blood sugar curves following the ingestion of dextrose for 16 nondiabetic children with certain diseases who had been confined to bed from six months to thirteen years, compared with typical sugar tolerance in active children.

To study this aspect of the problem further, the arterio-venous difference in the blood sugar was studied in 18 inactive adults and 16 inactive children and compared with the normal difference.

For practical purposes, a concentration of sugar in the blood obtained from the capillaries of the finger by a puncture is practically identical with the concentration of sugar in the blood simultaneously obtained from the radial artery. This has been demonstrated by various investigators. Consequently, in this paper I refer to sugar in the capillary blood as arterial blood sugar. The results of the tests for arterio-venous difference became quite significant after the ingestion of dextrose. This is illustrated in Chart 8.

In the inactive adults the usual arterio-venous difference in the fasting blood sugar was 8 to 10 mg. per 100 cc. A few had equal values for the arterial and venous blood sugar and in others the venous content was 3 to 4 mg. higher than the arterial.

At the peak of the curves after the ingestion of the glucose, the arterio-venous difference of the blood sugar generally ranged from 15 to 30 mg. per 100 cc. and on rare occasions the differences were as much as 40 to 50 mg. In three hours, the arterio-

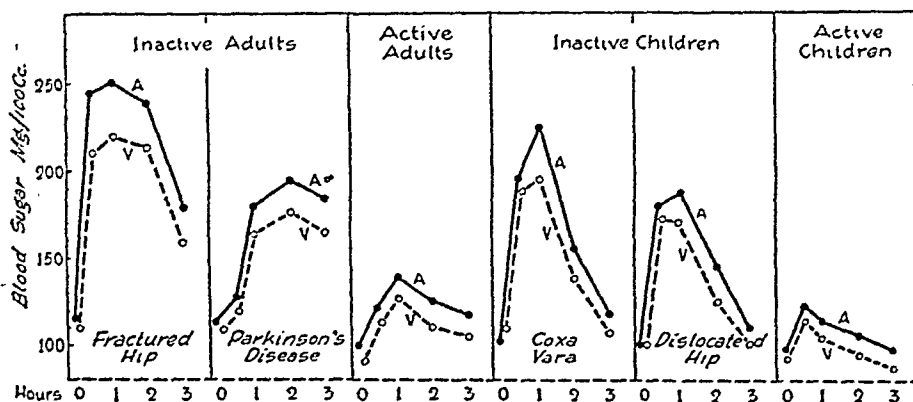


Chart 8.—Illustrations of capillary-venous differences in sugar tolerance curves for 18 adults and 16 children confined to bed for long periods, compared with corresponding values for active adults and children. A, capillary blood; V, venous blood.

venous differences were approximately 15 to 20 mg. In comparison, in the active adults after the ingestion of dextrose, the arterio-venous difference was 10 to 20 mg. at the peak of the blood sugar curves and approximately 10 mg. in three hours.

In children, the arterio-venous differences in blood sugar were similar to those in adults as illustrated in Chart 8. In many of the patients with diminished sugar tolerance, the arterio-venous differences were even greater than those ordinarily found in normal persons. This finding suggests that even though patients are physically inactive their muscles utilize sugar normally. No study on the rate of blood flow was made. This would be of interest.

It would appear that prolonged physical inactivity allows the pancreas to rest and results in sugar tolerance curves similar to those obtained when the pancreas is put at rest after insulin administration in the treatment of non diabetic malnutrition or when animals or individuals are placed on a high fat diet. Under these conditions the pancreatic islets are relieved of necessity for secreting insulin and the insulin content of the pancreas is reduced. Consequently, the reaction of the islets of pancreas to stimulation by dextrose becomes less than normal. Furthermore with physical inactivity there is not the demand for rapid storage and utilization of sugar that is present in active persons, and this results in

less demand on the pancreas, and ultimately in diminished function of the pancreas.

I believe that the reports of various authors showing diminished sugar tolerance in patients with certain diseases who have been ill for some time is not due to the disease in itself but rather due to the physical inactivity associated with these chronic diseases.

It appears that the diminished sugar tolerance noted in older persons is due not to age, but rather to the inactivity associated with age and that if these people were normally active their sugar tolerance would likely be normal. I have done the sugar tolerance test in a number of old active people with various diseases and found that their sugar tolerance was normal.

SUMMARY

This paper presents a study on sugar tolerance tests, methods, and evaluation. The methods discussed are the standard oral glucose tolerance test, the Exton-Rose Method, and the intravenous glucose tolerance tests.

Criteria for the diagnosis of diabetes mellitus, potential diabetes and renal glycosuria are given as well as for normal blood sugar curves.

A discussion is given of certain factors which may influence the sugar tolerance such as family history of diabetes, nationality, diet, infections, previous use of insulin, and prolonged physical inactivity.

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Discussion of Dr. Harry Blotner's Paper by Dr. Herman O. Mosenthal, New York City

It is a pleasure and a satisfaction to have heard Dr. Blotner's paper. The fact that the Clinical Society of the New York Diabetes Association has thought fit to discuss this matter of the interpretation of sugar tolerance tests dignifies this problem as one of serious import which is of interest to all practitioners of medicine and to insurance companies.

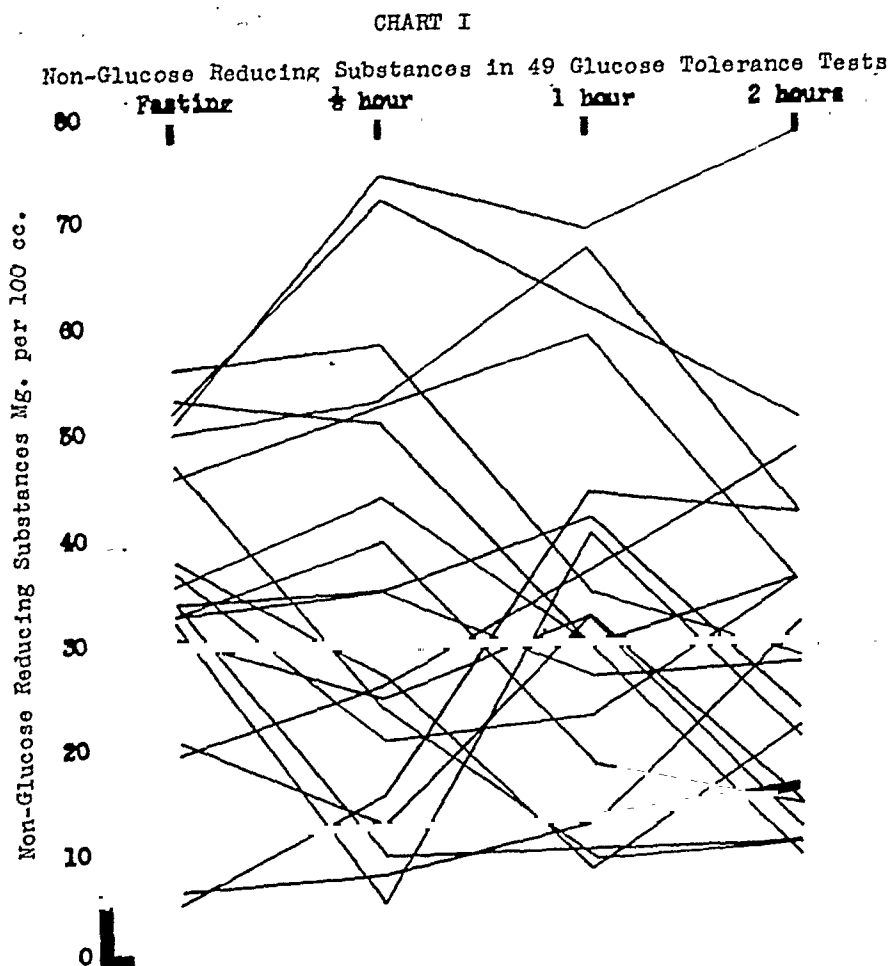
For some time past I have endeavored to determine how sugar tolerance tests could be improved for clinical application so as to make them more precise. All efforts in this regard accomplished little until Miss Barry and I three years ago began to evaluate the non-glucose reducing substances as reported as part of the Folin-Wu procedure, and also the arterio-venous B. S. difference.

What tests for sugar tolerance should one use? This is the first problem propounded by Dr. Blotner.

I am not in accord with Dr. Blotner's or others' ideas that this depends in a large measure on one's individual experience with a given test. This statement is based on the fact Chart 1 shows, that the non-glucose reducing substance that is the difference between the values obtained for true venous B. S. and those yielded by the Folin Wu method, are neither always of minor values, nor constant. The quantity, ordinarily supposed to be no higher than 30 mg. (according to some authorities no more than 20 mg.) is exceeded in about 40 per cent of glucose tolerance curves, yielding results which may be misinterpreted to a serious degree.

The arterio-venous B. S. differences in the experience of Miss Barry and myself are very much greater than those mentioned by Dr. Blotner. This is probably due to the fact that we have used the difference between the true arterial B. S. and the true venous B. S. and not the difference between the arterial B. S. and the B. S. yielded by the Folin-Wu method. As shown in Chart 2 in the fasting state the arterial and the venous B. S. approximate each other very closely, whereas at the one-hour period and the two-hour period the arterio-venous B. S. difference averages about 40 mg. per 100 cc. and may be as great as 100 mg. Since the observations in Charts 1 and 2 were made, some 60 further B. S. curves have been carried out in normal persons and verify the results given. Consequently we believe for the determination of the sugar tolerance the true venous B. S. should be used and the criterion which we believe to hold for this purpose, would be fasting B. S. 100 mg. per 100 cc. or less, the height of the B. S., that is in half to one hour 150 mg., and in two hours, 100 mg. or less. The renal threshold to glucose as has been stated by Peters and Van Slyke, Homer Smith and his colleagues, and Miss Barry and myself, can be judged correctly only by the arterial B. S.

For clinical purposes it must be recognized that the absorption of sugar from the intestinal tract is part of the function we are testing so that in the practice of medicine and for life insurance examination, it would seem preferable to the intravenous method. This is in agree-



Individual charting of non-glucose reducing substances of 20 glucose tolerance curves in which one determination exceeded the accepted upper normal limit of 30 mg. The heavy line is the average of non-glucose reducing substances of 29 glucose tolerance curves in which none of the determinations exceeded the accepted upper normal value of 30 mg. The variability of the non-glucose reducing substances not only from case to case, but also in successive determinations in the same case, is evident.

ment with Dr. Blotner's statements.

In judging the standards for interpreting the normal sugar tolerance test every one is agreed that the fasting B. S. should be normal, that is, from 100 to 120 mg., whatever test is used. The height to which the B. S. rises has been a controversial matter for interpretation. Dr. Blotner and Dr. Joslin's group in the past have laid great stress upon this feature of the curve. The Exton-Rose one-hour test depends upon the same criterion. As far back as 1920, MacLean of England said that a high curve, which he termed a "lag curve," but which was not prolonged, that is within normal limits within two hours, was not indicative of a diminished sugar tolerance. In 1925 I expressed the same opinion and in some follow-up work experienced that a high curve alone was not diagnostic of diabetes but that every case of diabetes had a high as well as a prolonged curve. This is a conclusion regarding which I have not had occasion to change my mind and am of the opinion, like a good many others, that every case of diabetes must have both a high and a prolonged curve, but that high curves alone do not constitute a reason for considering a sugar tolerance diminished.

Recently R. D. Lawrence of England expressed the same opinion. He put forward the thesis that what I call high curves and he called oxyhyperglycemic curves, were due to rapid absorption of glucose from the intestine and were not in themselves considered a sign of impaired sugar tolerance. Such interpretation of the high curve and, consequently, the unsatisfactory results yielded by the one-hour Exton-Rose test, have recently been accentuated by Lang-

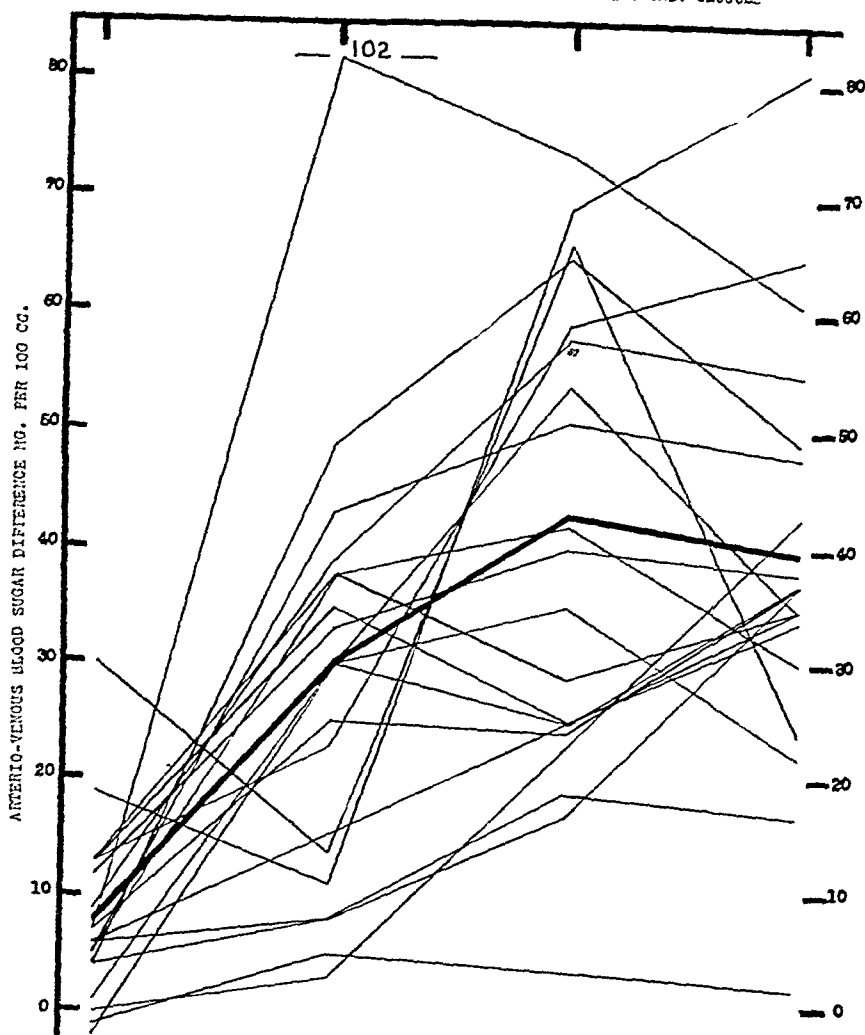
ner. The general opinion — which I share — appears to be that the value obtained at the end of two hours, next to the fasting B. S. level, is the most important measure we have in reading B. S. curves. For true venous B. S. this would be 100 mg. or less, for the Folin Wu method it has usually been set at 120, and for the arterial B. S. method according to our experience, it would be about 140 mg. The lack of security one must feel in using the Folin Wu method or the arterial B. S. method for the determination of the B. S. value two hours after the administration of glucose has already been mentioned. The advantage especially for life insurance companies in using arterial B. S. determinations or the Folin Wu methods, is that they will certainly not miss any case of diabetes though they may diagnose some normal persons as having diabetes, which is a very safe method for them to pursue but excludes some individuals from the privilege of obtaining life insurance, who should have it.

The unsuspected, high incidence of diabetes as was so ably shown by Dr. Blotner, in his analysis of selectees, is remarkable. In 1931 Dr. Alice Paulsen surveyed the cases of diabetes discharged from 24 hospitals in New York City, and found that of 1617 cases of diabetes treated in these institutions, 318 (nineteen per cent) were diagnosed only after admission to the wards for treatment of some other ailment. All these observations go far to show that our methods of diagnosing diabetes have been and are very far from satisfactory and should be improved upon.

The interpretation of the significance of these unexpected glycosurias apparently varies a great deal. Dr. Blotner

CHART II

ARTERIO-VENOUS BLOOD SUGAR DIFFERENCE AFTER 100 GMS. GLUCOSE



The marked rise of arterio-venous blood sugar difference after the taking of glucose is evident. The average difference (heavy line) is 8 mg. per 100 cc. fasting, and 40 mg. two hours after glucose ingestion.

found in one of his series less than ten per cent incidence of renal glycosuria. Dr. Lawrence in his series of 800 cases of glycosuria in army personnel, found sixty-five per cent of renal glycosuria. In my own experience with cases of doubtful glycosuria, published in 1925, I found 22 out of 37 cases, about sixty per cent, gave evidence of renal glycosuria. It would seem to me that probably Dr. Blotner's interpretation of the height of the curve as indicating diabetes is the reason for these varying results. The importance of obtaining arterial B. S. for the determination of the renal threshold to glucose is shown in Chart 3. Here it may be noted that the arterial B. S. may rise while the venous B. S. drops. This is shown in the half to one-hour period in the above two curves. Under these circumstances the interpretation of the renal threshold to glucose is inaccurate when judged according to the venous B. S. It is probable that this phenomenon is responsible for the impression that the renal threshold to glucose is lower when the venous B. S. falls than at the onset of the curve when it rises. Judged according to the arterial B. S. the renal threshold to glucose is directly proportional to the arterial B. S. level.

Two cases of renal glycosuria worthy of record because of their known long duration without progress into true diabetes, are as follows:

J. G., male. Sugar found on life insurance November, 1922 when 19 years of age. Normal glucose tolerance curve; diagnosed as renal glycosuria. Checked in January, 1939 and in April, 1947, and the same condition found. Hence in 25 years, there has been no change in the diagnosis; there have been no untoward symptoms.

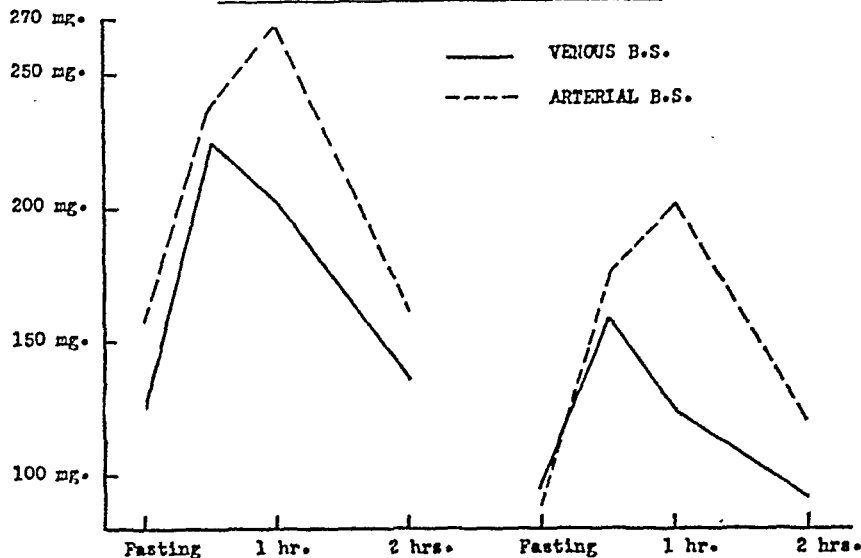
J. R., male, age 50. Diagnosed as renal glycosuria in 1913 by Dr. F. Gorham Brigham of Boston. Checked at intervals, the last time by me in April, 1947, when he had a normal glucose tolerance curve and exhibited glycosuria with a low renal threshold. Duration 29 years without production of untoward symptoms or the development of diabetes.

There is some dispute as to whether the renal glycosuria may be acquired or whether it is a congenital disturbance of the function of the renal tubules. At the present time I have four cases of diabetes which have developed a low renal threshold, that is, they have acquired a renal glycosuria in addition to their diabetes.

There was one case which established beyond doubt that renal glycosuria could be acquired for no apparent reason at the age of 66, and that in over five years subsequently the condition persisted and did not change into or exhibit any signs of diabetes mellitus. This patient, a physician, had for 20 years examined his urine about

CHART III

DIVERGENT TRENDS OF ARTERIAL VENOUS B.S.



Arterial B.S. may rise while the venous B.S. drops. This is shown in the half to one hour period in the above two curves. Under these circumstances the interpretation of the renal threshold to glucose is inaccurate when judged according to the venous B.S. It is probable that this phenomenon is responsible for the impression that the renal threshold to glucose is lower when the venous B.S. falls than at the onset of the curve when it rises. Judged according to the arterial B.S. the renal threshold to glucose is directly proportional to the arterial B.S. level.

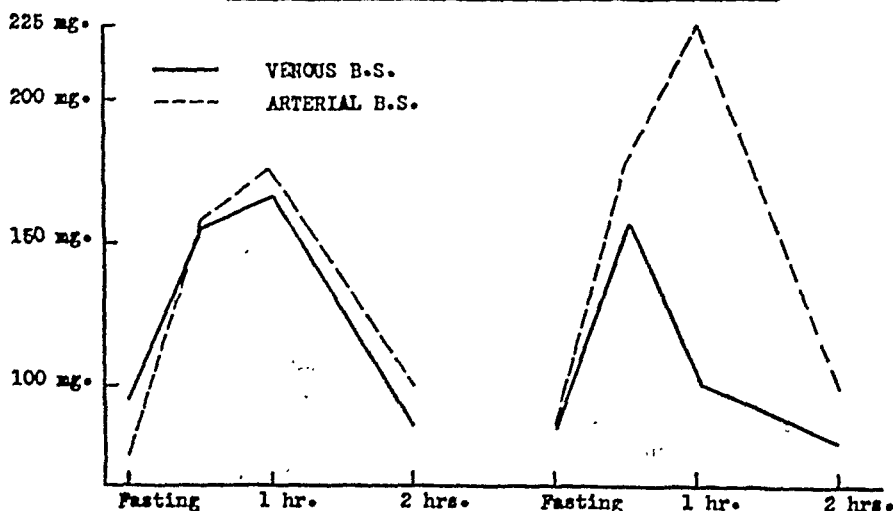
every two weeks for the purpose of using his specimen as a normal control test while carrying out life insurance examinations. At the end of this period glycosuria appeared. He proved to have constant traces of sugar in his urine with a blood sugar of .120 mg. per 100 cc. and higher. He subsequently ate as his fancy dictated, including sugars. Five years later at the age of 71 he was feeling well and carrying on the practice of medicine successfully. During these five years the glycosuria persisted

in traces but there have been none of the other accepted signs of diabetes mellitus.

Miss Barry and I have been carrying out observations on normal persons and have found that in the old age group, contrary to our expectations, we have obtained normal glucose tolerance tests. The finding of Blotner that rest as carried out in a hospital patient, is productive of a diminution in the sugar tolerance, accounts for the fact that so many observers have found sugar toler-

CHART IV

What does a GLUCOSE TOLERANCE TEST DETERMINE?



Two blood sugar curves illustrating two different means of utilizing B.S. In the right hand curve the arterio-venous B.S. difference is marked pointing to diffusion of sugar into the peripheral tissues. In the left hand curve the arterio-venous B.S. difference is slight showing that the assimilation of sugar did not take place in the peripheral tissues but elsewhere (liver?). Consequently there are at least two processes by which a normal B.S. curve may be achieved and there are possibly others. Which of such processes are impaired when a diminished sugar tolerance occurs remains to be determined.

ance diminished in the aged. In Miss Barry's and my experience thus far in older persons who are up and about and active, we have failed to note any diminution in the sugar tolerance though some time ago Dr. Deren, under our supervision working on hospital patients, did find impaired sugar tolerance in the aged, while at the same time Drs. Short and Johnson working at the Life Extension Institute (in active persons) failed to demonstrate any diminution of sugar tolerance in older people. The findings of Blotner that sugar tolerance tests must be carried out in persons who are active and not confined to hospitals or institutions therefore should be borne in mind when glucose tolerance tests are carried out.

The mode of the disposition of glucose after absorption may be determined, to a certain extent, by the simultaneous determination of true venous B. S. and true arterial B. S. Chart 4 demonstrates this. Two blood sugar

Discussion of the Paper by Harry Blotner, M.D., by Edgar W. Beckwith, M.D. Medical Director --- Equitable Life Assurance Society

When Dr. Shlevin invited me to discuss Dr. Blotner's paper, I advised him that I would be pleased to do so, but that my opinions would of necessity be presented from the standpoint of life insurance medicine. Therefore, I wish to have it clearly understood that my approach to this question is not that of the clinician, but is that of a medical officer of a life insurance company. On the one hand, there are certain considerations which constitute common ground for both of us, but on the other hand there are other considerations which are necessarily different since they arise from different concepts related to the problem of evaluating the significance of glycosuria.

With your indulgence, before entering into a detailed discussion of the paper, I would like to paint a general background concerning basic differences of viewpoint. Fundamentally, we are all doctors, and therefore scientifically inclined, even though, of necessity, our paths may sometimes diverge; and, although we should not be on different sides of a fence, at the same time, it is reasonable to examine the question objectively, and to scrutinize the reasons underlying a different approach to the problem.

In a review of this nature, I should like to compare the position of the clinical specialist with that of a life insurance medical officer, and also to comment on the practice of companies in general, but with especial reference to the procedure with which I naturally am most familiar, viz.:—that followed by my own company, the Equitable Life Assurance Society of the United States.

The clinical specialist is usually confronted with a situation, in which the patient (often referred by a general practitioner who feels that he has inadequate knowledge of a complicated problem) comes for consultation, either because he has symptoms of diabetes, or, because during a routine health or life insurance examination, glycosuria has been discovered. The specialist is called upon to answer three questions: 1—Has the patient diabetes? 2—If so, can the severity of the disease be estimated? 3—How successfully can the condition be controlled by diet, insulin, or other measures? Admittedly, the clinician is sometimes under pressure to furnish categorical answers to these questions with promptness. The answer to the first question is not always easy, because of the various criteria proposed by different observers, which differences are so well exemplified in Dr. Blotner's paper. However, in dealing with the other two questions, the clinician usually has a reasonable amount of latitude in pursuing a trial and error method. In answering the first basic question, he may express an opinion that the person is diabetic, or non-diabetic, or he may, with entire honesty, because of borderline findings, use the terms "pre-diabetic" or "potential diabetic," or other similar expressions which are in common use,

curves illustrating two different means of utilizing B. S. In the right hand curve the arterio-venous B. S. difference is marked pointing to diffusion of sugar into the peripheral tissues. In the left hand curve the arterio-venous B. S. difference is slight, showing that the assimilation of sugar did not take place in the peripheral tissues but elsewhere (liver?). Consequently there are at least two processes by which a normal B. S. curve may be achieved and there are possibly others. Which of such processes are impaired when a diminished sugar tolerance occurs remains to be determined.

From our experience we believe that impaired sugar tolerance is usually accompanied by a depression of both of these functions, that is the assimilation of sugar by the peripheral tissues as well as in the liver. The idea variously expressed that either the liver or the peripheral tissues is an exclusive factor in the type of B. S. curve would not seem to hold good.

but which actually constitute, at that juncture, an admission of inability to make a positive diagnosis. Such an admission is readily understandable in view of the factors inherent in the disease itself, and hence the obvious fact that only the passage of time will supply the final answer. Furthermore, the clinician usually has the opportunity to observe his patient over a period of time, and to revise his opinion at a later date, if the patient remains under observation.

On the other hand, a life insurance medical officer is in a quite different position. Since he is compelled to evaluate a risk expressed in terms of a certain amount of money, and, in reaching his decision, he has to rely on data which might well be regarded by a clinician as meager. Admittedly, in the same way that the clinician has for his guidance his own experience and also published statistical data, the medical officer has the benefit of certain criteria based on the so-called "experience" of his own and other companies. The "experience" reflects the ultimate results derived from having insured many individuals with a similar impairment over many preceding years. His decision involves either acceptance of the risk at standard or substandard premium rates, or rejection of the risk. However, the point which I wish to stress is that, once his decision has been made that the risk is acceptable on some basis, and hence the company enters into a life time contract with the individual, he rarely has an opportunity to evaluate the validity of his original judgment, except under the following circumstances:—

1—If the individual applies for insurance at a later date, and, perforce, submits to a physical examination, and hence to a new evaluation of the problem of glycosuria in his particular case.

2—If the policy lapses for non-payment of the premium, and the insured applies for reinstatement, and hence is again examined.

3—If the policy matures as a death claim, and it comes to the attention of the medical officer, assuming that he is alive and employed.

A fundamental difference in the two approaches lies in the fact that the clinician deals primarily with the individual, and, even though his practice is large and he himself lives to an advanced age, and he is successful in obtaining later observations on many patients, nevertheless, his statistical data must almost necessarily be obtained from a relatively small group. On the other hand, an insurance company, by the very nature of the theory of insurance, deals with the average results obtained from insuring large groups of people, and hence obviously cannot predict the outcome in a single individual. Furthermore, the company continues to exist indefinitely, and also, with respect to insured lives, the

company knows the age at death and the cause. Considering the above factors, it should be readily understood, that, as medical officers we cannot indulge in the use of such terms as "potential diabetic," except as a matter of conversational convenience, but, on the contrary, we must develop and apply a formula which enables us to select risks on a satisfactory basis regardless of the terminology employed. Admittedly, criteria change with advancing knowledge, and hence the formula must change, but the point which I wish to emphasize is that at all times we medical officers must have a formula which takes into account the various factors involved in evaluating the insurance risk, and, in my own opinion, the glucose tolerance blood sugar test, is the most valuable single criterion according to our present day knowledge.

Parenthetically, practically all companies use a numerical rating system which permits credits for favorable factors and assesses debits for unfavorable factors, and such a system lends itself well to the application of a formula involving credits and debits in dealing with glycosuria.

I must admit, with some reluctance, that the variation in company practice, both with respect to obtaining data, and evaluating the risk, is probably quite comparable to the degree of variation among clinicians with respect to diagnosis and treatment. This variation is especially unfortunate, because, as everyone knows who had dealt with statistics, homogeneity of the material under consideration is a most important consideration.

Generally speaking, the practice of companies is to issue relatively small amounts of insurance based on urinary findings alone, although the companies do require post prandial specimens, and base their conclusions on the incidence and percentage of glucose found. This procedure is primarily unsound in not detecting cases of renal glycosuria. But, on the other hand, frequently cases of renal glycosuria are aware of their condition, and are willing to prove it by submission to a tolerance test. Furthermore, if the applicant is rated or declined because of urinary findings, he consults a specialist. All companies draw the line at some amount of insurance at risk, and above this amount they require a blood sugar determination of some sort. Some companies, almost unbelievably, rely on a fasting blood sugar alone; others require some type of tolerance test, using from 50 to 100 grams of glucose, but are interested only in the fasting finding and a single other finding at the end of either one and one-half, two, or two and one-half hours. Still others, which to my mind are on the soundest ground, require a more or less classical tolerance test, with blood and urinary findings at intervals (a) fasting, (b) one half hour, (c) one hour, (d) two hours, and rarely (e) three hours. A further complication arises out of the fact that many companies, without adequate Home Office facilities, employ local laboratories and do not specify the technique to be employed, either as to the source of the blood or the chemical method employed. The fallacious results obtained by employing such heterogeneous methods can well be imagined after considering the data presented by Mosenthal about a year ago in his paper on "Evaluation of Blood Sugar Tests" and published in the "American Journal of Digestive Diseases" in May 1946.

I wish to outline briefly the procedure in my own company, the Equitable Life Assurance Society, which was initiated in 1925, at which time, we were practically pioneers in the field of insuring glycosurics, and which procedure, with a few modifications is still in force. We arbitrarily require glucose tolerance blood sugar tests where the amount exceeds \$10,000 at risk; we accept no tests performed by outside laboratories, and insist that specimens be examined in our Home Office laboratory; we use 75 grams of glucose, capillary blood, and the Folin Micro chemical method. The material is obtained by the original examiner, and mailed to the Home Office in a

specially prepared box with vials for blood and urine containing proper preservatives. We obtain specimens (a) fasting, and at (b) one half hour, (c) one hour, (d) two hour periods. Our method might be criticized as to the amount of glucose employed and other matters of technique, but, at least, it has produced homogeneous data for statistical purposes, which is a prime consideration in life insurance statistical studies. In arriving at an underwriting evaluation of the risk, our particular formula contemplates almost exclusively the behavior of the blood sugar curve during the second hour. At the risk of repetition, I again emphasize the fact that, from our standpoint, there are three important factors:— 1— The glucose can be readily administered and the test material obtained by any practitioner, even though not versed in laboratory skill. 2— The material is all examined in our own laboratory under standardized conditions. 3— The selection of the risk depends on a formula which is an arbitrary device. However, even though the device is arbitrary, a study of our own mortality statistics involving 10,000 insured lives, and also a follow up study, which we conducted on 2200 individuals (1800 rejected by us and 400 who refused the offers made), with information received on 94 per cent, has proven the soundness of our formula from the standpoint of insurance selection. No formula of this nature can be entirely perfect, and any formula may occasionally exclude a desirable risk, or include an undesirable one, but, in dealing with the general law of averages, our formula appears to have been fair in its operation both with respect to the applicant and to the company, which, in a mutual company such as ours, means the other policyholders.

After this somewhat lengthy outline of the difference in our approach to this problem, I would like to express a few detailed comments on Dr. Blotner's admirable paper. In a very general way, I agree that the combination of "marked glycosuria and considerably elevated blood sugar" justifies a diagnosis of diabetes, even though the terms employed are relative. However, it seems to me that no physician should be satisfied with a single observation of this nature, except under emergency circumstances, and it should be almost mandatory to perform a tolerance test at least once before making a definite diagnosis. As Wilder has pointed out, if a clear cut diagnosis has been once established by a tolerance test, observations of fasting blood sugar findings are adequate and valuable in evaluating control and progress. The value of a tolerance test is, of course, obvious in segregating the not uncommon cases of renal glycosuria. Parenthetically, I would remark, with reference to particular criteria, that we have a few individuals whom we insured at standard rates about 20 years ago, based on the opinion of eminent specialists at that time that they were renal glycosurics, who subsequently demonstrated that they were true diabetics. I agree with the author that tolerance tests should be done under controlled conditions, and I may add that a highly desirable goal would be a standardized technical procedure to be observed by all concerned. Dr. Blotner expresses his opinion that the safest criteria in interpretation are a combination of the peak and rate of fall of the curve. He refers to the somewhat variable criteria laid down by various observers, and probably the most stringent are those defined by Joslin. Hence, it is with some understandable temerity, in speaking of our Equitable Life practice, that I make a statement which may seem unorthodox to my clinical brethren, and that is:—that we are not too greatly concerned about the fasting blood finding unless it exceeds 130, nor are we greatly concerned about a peak unless it exceeds 250 at the end of one hour. These criteria are quite different from those laid down by many clinicians, but our principal interest lies in the rate of delay of the curve during the second hour, because in our experience in selecting risks this appears to have been a satisfactory method of judging the ability of the pancreas to mobilize insulin. In my

own experience, however, during the past 15 years of personal scrutiny of many of these cases, I have observed that it is very uncommon to see a case which either exceeds 130 fasting, or 250 at the end of one hour, which does not, at the same time, show a markedly delayed fall during the second hour and hence is not insurable under our rules. On the other hand, it might be surprising to you to see the number of cases that show a fasting finding of 90-120, and a peak as high as 230, but which at the same time fall rapidly in the second hour to a point below 140. In the parlance of the present day, this might be regarded as delayed mobilization of insulin, but, at any rate, for our purposes, and in applying our formula, regardless of the peak, we consider a curve which reaches 140 or below at the end of the second hour as either "normal" or "equivocal." The difference between the two latter terms is determined by the rapidity of fall, and, the more rapid the fall, the greater the credit granted in our evaluation. I was interested in the author's comment on the well known fact that restriction of diet for some days preceding the test may give rise to fallacious results. We occasionally see cases in which we have knowledge of previous tolerance tests performed over a period of several years, and in which the current test is definitely less favorable. Under these circumstances, the question arises as to whether the person's condition is actually deteriorating, or whether, being ignorant of the real effect of dietary restriction, the person has attempted to prepare himself for the test by limiting his carbohydrate intake for several days, thus producing a result which is actually to his disadvantage.

Referring to types of tests, I believe that the standard test with oral administration of one dose of glucose is the most satisfactory. The Exton-Rose, two dose, one hour test should have certain advantages from a "business" standpoint because of the lesser period of time required. However, this test is rarely used by any of the companies, perhaps because of the fact that it has never attained widespread usage, and consequently the volume of statistical material obtained from observations by this method is rather meager. However, this is only surmise on my part. As far as I know, the intravenous glucose test has never been used by the companies for the basic reason that we are precluded from doing any type of test which involves any possible hazard to the individual, such as any intravenous administration, cystoscopy, spinal puncture, etc. — the principle being that the individual might allege that he had been harmed by the procedure and a suit for damages might result.

The results of studies made in selectees are indeed of great interest, especially because of the large size of the group under observation. Obviously, the amount of effort expended in performing the tests and in evaluating the results statistically must have been very great, and Dr. Blotner is to be complimented for a very commendable piece of work. Judged by the

Equitable Life's experience, the criteria seem to me somewhat stringent, but I thoroughly agree with him that routine urine tests among the general population would be highly desirable, and should result in the discovery of hitherto unsuspected cases of diabetes. In life insurance practice, not infrequently, we observe cases in which the first intimation which the applicant gains that his condition is not normal arises from the results of the medical examination made in connection with his insurance application. To the best of my knowledge, no studies have been made by the companies as to the effect of nationality, but the influence of family history has long been regarded as a potent factor. I know of one company that requires a tolerance test in all applicants showing a certain degree of overweight and with a history of diabetes in parents or siblings.

With reference to renal glycosuria, our criteria contemplate a curve which does not rise above 140, remains below a chart line drawn from 140 to 125 during the second hour, with positive urinary findings in all specimens, except the fasting one, which may or may not be positive. The tolerance test is of importance in clinical practice to discover these cases, and hence demonstrates the fact that no treatment is necessary, and, by the same token, the test is of importance in insurance practice, because otherwise the applicant might be unjustifiably either declined or charged an unwarranted extra premium.

I am not in a position to comment on the author's interesting remarks concerning the effects on tolerance produced by diminished physical activity associated with various chronic diseases, or age, because of the obvious fact that persons in this category are not applicants for life insurance.

I do not wish to seem too critical, but the conclusions drawn from the investigation of the arterio-venous differences in this group may be of dubious validity, because a comparison is made with the figures generally accepted as being correct in a so-called active group. The fallacy in this procedure, as well demonstrated by Mesenthal in the paper previously referred to, and in which he showed that, in a series of 200 consecutive determinations, (admittedly mostly in diabetics but with some normals included) over one third showed a difference in excess of the usually stated figure of 20 mg.

In conclusion, may I again stress the fact that, while some of my comments may seem unorthodox to you as clinicians, they have been offered by me in my capacity as a medical officer of one of the largest insurance companies, and that the utilization of our criteria has been successful as a means of selecting risks among a large number of glycosurics with, what we believe to be, a maximum degree of fairness to all concerned. I wish to compliment Dr. Blotner on having made a valuable contribution to the literature, and also to express my opinion that all of us should strive to utilize standardized procedures in order that the conclusions drawn from our observations may have the greatest statistical validity.

The Eye in Diabetes

By

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THE PROPER EMPHASIS on visual disturbances occurring in patients with diabetes mellitus has frequently been given. Many writers have stressed the transitory changes in refraction dependent upon changes in the index of refraction of the crystalline lens initiated by changes in the sodium chloride

content of the aqueous and osmotic interplay following blood sugar shifts. Others have spoken of the fact that retrobulbar neuritis is more common in the diabetic than the non-diabetic. Cataract has been shown to be no more frequent in the diabetic than the non-diabetic and that only the juvenile patient with subcapsular opacifications can be said to have a true diabetic cataract. Finally the inroads of retinopathy

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on vision through hemorrhages, waxy exudates and complicating vitreous hemorrhages with its sequelae retinitis proliferans and detached retina have been sufficiently spoken of in both ophthalmological literature as well as that dealing primarily with internal medicine to make the average medical man conversant with the above pathology.

The purpose of this paper is rather to stress the interpretation of the eye findings in terms of general mechanisms acting in diabetes and to point out the pathogenesis of diabetic retinopathy as it is regarded today.

The earliest sign found in the retina in diabetes is retinal venous dilation. Mylius (1) in 1937 was one of the first to call attention to the fact that this venous stasis in the finest capillary network with consequent nutritional changes was fundamental in the development of diabetic retinopathy. In this country Agatston (2) was likewise an early proponent of this theory and demonstrated in more advanced cases histological evidence to back his contention.

This sign however is somewhat equivocal. The first unquestionable sign to appear is pin-point hemorrhages in the macular region or at least the posterior pole of the eye. Ballantyne (3) has shown that many of these are minute globular aneurysmal dilations of the capillaries. Anatomically Quain (4) has shown that the retinal arteries lie in the nerve fibre layer and give off twigs which form two capillary networks, one the fibre and ganglion cell layer, the second in the inner nuclear layer. These are connected by intervening capillaries, the inner network is connected with the arteries and the outer, the veins. The aneurysmal dilations of Ballantyne are distentions of the capillaries which form the link between the precapillaries on the arterial side and those on the venous side. Histologically the endothelial cells of the capillaries are filled with fatty granules and probably dilate from the venous stasis acting on the diseased capillaries. The majority of the pin-point spots seen however are true hemorrhages occurring in the inner nuclear layer.

That these hemorrhages may occur without any evidence of arterio-sclerosis that is discernible with the ophthalmoscope is best attested to by the findings in the young diabetics. This past summer a survey of 127 juvenile diabetics was undertaken at Camp NYDA. Three patients aged 12, 15 and 15 had had diabetes 8, 11, and 9 years respectively and each showed pin-point hemorrhages and venous dilation with no arterial changes. In no case were exudates seen which suggests that hemorrhages precede the appearance of the waxy exudates. These hemorrhages may appear and disappear as do occasionally the exudates. The latter are dependent upon nutritional changes and appear in its early phase as pin-point lesions as do the hemorrhages. Ballantyne believes some of these are due to thrombosis of the earlier aneurysmal dilations. The majority are probably not and are secondary to the capillary changes nutritionally and seen characteristically in the outer plexiform layer. I have frequently seen such exudates in the non-diabetic eye in cases where an oedema

secondary to an inflammatory focus or a closed vessel had caused an interference with retinal nutrition. In both types of cases such exudates absorb gradually leaving no evidence of their presence. These exudates in diabetes may coalesce and form larger waxy exudates, but do not take on the star shaped configuration one sees in albuminuric retinitis (fig. 1).

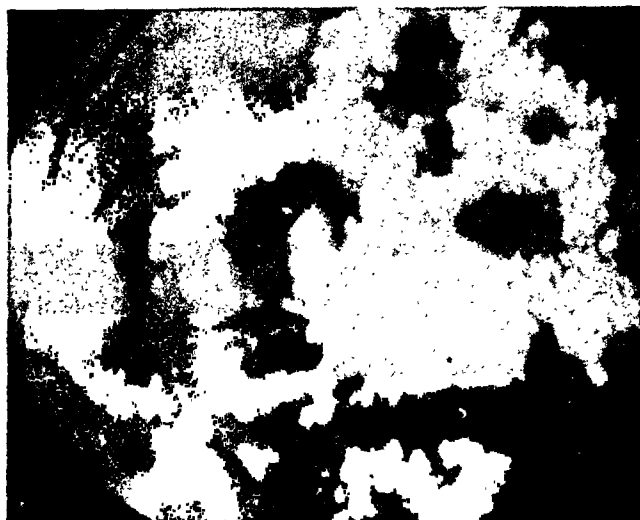


Fig. 1 — Massive waxy exudates in the macula region in a diabetic with retinal arteriosclerosis.

Studies are now being carried out histochemically to determine the nature of the fats deposited whether they are phospholipins or the like.

This picture constitutes the early characteristic picture of diabetic retinopathy. In regard the frequent association of retinal arterio sclerosis, it is well known and recognized that diabetes leads to early premature arterio-sclerosis and with its advent other findings are added. In about 5 per cent of cases marked phlebosclerosis is the outstanding pathology (fig. 2).

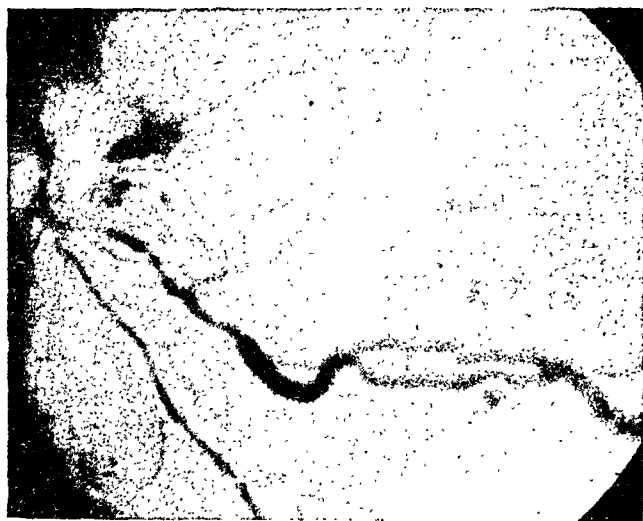


Fig. 2 — Marked retinal phlebosclerosis in a diabetic of 17 years duration.

Wagener has pointed out his so-called mixed hemorrhagic retinitis in which the superficial flame shaped hemorrhage predominates in the picture. This type he believes is dependent on vascular and renal shange.

What brings about this early dilation of the ter-

diabetic patient is proposed, insisting that every diabetic patient have a complete eye examination and no diabetic fundus be considered negative unless it is studied under a mydriatic.

Duration of the disease is important for as Dolger (6) stated in a study of 200 patients below 50 years of age followed for 25 years none escaped without retinal hemorrhages and a hypertension in varying degrees. In another communication he again noted that 50 per cent of patients having retinal hemorrhages will have albumin in the urine. These findings stress the significance of the retinal findings and warrant further observation along these lines.

The reason for including E. C. G. would be to substantiate a claim made that "every patient 40-50 with marked retinal disturbance showed electro-cardiographic evidence of myo-cardial degeneration" (10). Cholesterol is included as a sign of control bearing in mind also Joslin's observation that a low cholesterol has not a good prognostic import. It is quite possible with the above factors tabulated by the same observers when that can be done, valuable information for further statistical deduction will be had.

A word on the use of the slit-lamp in the study of the diabetic patient is in order. I have omitted arcus senilis which occurs in 39 per cent of diabetics, the same percentage as the non-diabetics. Likewise no space has been left for pigmentation on the posterior surface of the cornea which occurs more than twice as often in the diabetic due to the facile release of pigment from the epithelium of the iris probably dependent upon the deposits of glycogen in this layer of the iris. In the study of the pupil by transilluminated light played from the lens such depigmentation might be observed and recorded.

Attention is called to a better study of the conjunctival vessels in the diabetic, an examination that is not routinely done even by ophthalmologists. Recently a rare observation was made on a patient with retinal phlebosclerosis associated with a diabetes of 17 years duration in that the aqueous vein showed phlebosclerosis.

Ascher, who has made ophthalmologists cognizant of the presence of aqueous veins, in a personal communication wrote he had never seen a like occurrence. Ruedemann (11) and others have studied and photographed changes in the conjunctival vessels in various vascular diseases. In regard the plica, here one can observe the capillaries and study them under at least a 40 magnification (fig. 3). Not infrequently

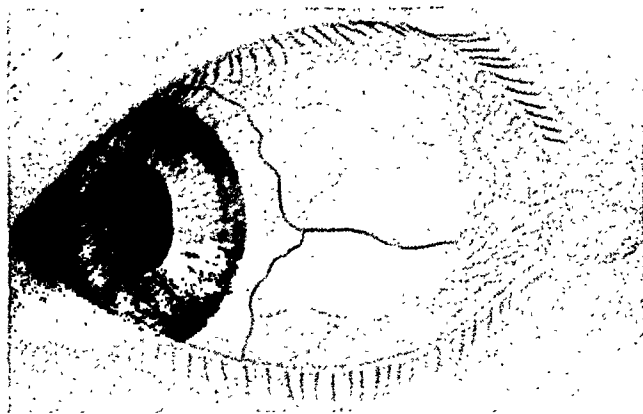


Fig. 3 Capillary dilation in the plica semilunaris as seen in a juvenile diabetic.

these vessels will be dilated when the remainder of the conjunctiva is normal as far as absence of congestion is concerned. Most of the cases seen with dilation of the small capillaries and vessels on the face will show the dilation here. On the other hand there is no correlation of the capillary dilation and the retinal capillary dilation as one will observe marked pathology in the retina and normal surface capillaries and vice versa. The part exposure works on the capillaries will have to be better worked out.

In conclusion one should not consider that there is no more to add to the picture of diabetes in the eye than was observed 75 years ago, but with the advent of newer instruments and newer interpretations of physio-pathology in diabetes try to harmonize the findings with the more modern concepts of the disease.

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The Effect of d-Desoxyephedrine upon the Prothrombin Time

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ONE OF THE newer drugs to inhibit gastric contractions in order to attenuate the sensation of hunger and therefore reduce the appetite is the dextro-rotatory isomer of Desoxyephedrine (1). Since undernutrition predisposes to hepatic degenera-

tion (2), it is of utmost importance to determine the effect upon the liver of any drug used in the management of obesity, in conjunction with a reduced caloric intake. Just as an earlier study (3) demonstrated that desiccated thyroid in the usual therapeutic doses has no deleterious effect on the liver,

so it is demonstrated in this paper that d-Desoxyephedrine is a therapeutically safe weight-reducing drug as determined by prothrombin estimation.

This drug, an analogue of amphetamine, possesses an appetite reducing action free from the peripheral vascular effects of racemic amphetamine when given in therapeutically active doses. The average dose of d-Desoxyephedrine used in this series was 7.5 mg. per day; one tablet (2.5 mg.) was given before breakfast, and two (5.0 mg.) before lunch.

HEPATIC FUNCTION TEST

Prolongation of the diluted (12.5 per cent) plasma prothrombin time is a sensitive index of the early detectable functional changes demonstrable in liver disease. This prolongation occurs clinically in man (4, 5, 6), and it has been induced in dogs by carbon tetrachloride. Other tests of hepatic dysfunction, including bromsulfaphthalein retention have been found to be less sensitive than the prothrombin test.

The elaboration of prothrombin is a reflection of the functional condition of the liver, and if hypoprothrombinemia fails to disappear after adequate doses of Vitamin K, functional hepatic pathology is likely.

METHOD OF PROTHROMBIN ESTIMATION

The procedure used is the one described in earlier communications (7, 8). The prothrombin time of both whole and diluted (12.5 per cent) plasma is estimated. The test calls for a thromboplastin of a high standardized potency. A preparation of desiccated fresh rabbit lung has proved most satisfactory in our hands. The technic establishes a precise and unmistakable end-point by the lifting of the clot the instant it forms from the otherwise clear fluid.

The normal standards are as follows:

Whole plasma prothrombin time . . . 14-17 seconds.

Diluted (12.5 per cent) prothrombin time . . .
37-42 seconds

All estimations are made in duplicate after maintaining the plasma at body temperature for 15 minutes.

MATERIAL AND PROCEDURE

Twenty patients varying in age from 12 to 62, of whom thirteen were females, constituted the present series. All were cases of obesity in which medication with a calorogenic agent such as a desiccated thyroid was contraindicated because of intolerance to the drug or the presence of adverse symptoms such as tachycardia, hypertension or increased basal metabolic rate. No medication other than d-Desoxyephedrine was administered. A diet adequate in protein content which varied between 1100 and 1400 calories was prescribed. While no vitamin K was added, a vitamin B Complex preparation was generally advised. Leafy vegetables were permitted according to individual desires.

MEDICATION

Three groups of four patients each received the medication for eight, six and four weeks respectively.

One patient received the drug for twelve and one for seven weeks. Two groups of three patients took the medication for a period of ten and five weeks respectively.

The behavior pattern of all the patients developed with remarkable consistency. Initially there was enthusiasm and cooperation. The patients would restrict their food intake and their weights would show a sharp reduction. As the weeks passed, the enthusiasm waned, the weight loss ceased, and the patients sheepishly confessed that there had been some "cheating." Apparently the fundamental neurotic compulsion had been making abstinence from food more and more difficult.

At this point the d-Desoxyephedrine was introduced into the therapy. It was found very important to impress upon the patient the belief that this medication would be effective in its attenuating action upon the desire for food. While no study was made with a placebo substitute, the fact that it was necessary in more than half of the cases to increase the dose from an initial 5 mg. to 7.5 mg. per day to obtain the desired effect seeks to support the view that the drug action was in some measure necessary to obtaining weight reduction.

No evidences of toxicity such as further acceleration of the pulse, alterations in electrocardiographic tracings or increases in blood pressure developed. The chief source of relief noted after the weight loss, especially where an abnormal circulatory pattern was already in existence, was greater ease in breathing, particularly after exertion.

PROTHROMBIN RESULTS

All of the cases showed normal prothrombin time of both the whole and the diluted (12.5 per cent) plasma prior to the treatment. Prothrombin estimations were made once weekly for the first two weeks and once a month thereafter. Throughout the period of treatment the prothrombin time estimation of all the cases remained within the normal range. In one case (No. 3) the prothrombin time of the diluted (12.5 per cent) plasma was moderately prolonged at the period of initial pronounced weight loss. This prolongation disappeared spontaneously in the course of the treatment.

COMMENT

d-Desoxyephedrine administered over significant periods and resulting in the desired loss of weight, is attended by no increase in the prothrombin time of the whole or the diluted (12.5 per cent) plasma. In every case the food intake was adequate from the standpoint of protein and components of the vitamin B Complex. One patient showed a temporary hypoprothrombinemia during a period of marked weight loss when the diet had a low caloric content. Apparently the hypoprothrombinemia resulted from K vitamin and nutritional deficiency because the prothrombin time recovered to normal when food intake increased. Medication was continued through the period of hypoprothrombinemia. This is supporting evidence that d-Desoxyephedrine exerted no effect upon the prothrombin elaborating system.

Initials	C	A	S	E	No.	Sex	Age	Duration of Medication	Diluted (12.5 per cent) Plasma Prothrombin Time (Seconds)		Diagnosis and Remarks
									Before	After	
L. K.					1	F	42	12 weeks	41.5	39.5	Paroxysmal Tachycardia
M. S.					2	F	54	10 weeks	38.0	39.5	Hypertension. Hyperexcitability.
I. S.					3	M	28	10 weeks	39.0	38.0	Tachycardia after previous thyroid therapy.
N. M.					4	F	56	8 weeks	39.5	39.5	Hypertension
N. F.					5	F	12	10 weeks	40.5	39.0	Tachycardia
B. L.					6	M	40	8 weeks	37.5	39.5	Palpitation after desiccated thyroid
S. W.					7	F	48	5 weeks	40.5	43.5	Menopause. Anxiety neurosis
R. T.					8	F	49	4 weeks	40.0	39.5	Post-thyroidectomy
P. D.					9	M	62	6 weeks	38.5	37.6	Overindulgence and obesity
E. C.					10	F	20	8 weeks	39.5	40.5	Tachycardia after thyroid therapy. Palpitation
E. M.					11	F	58	8 weeks	38.0	44.0	Headache after thyroid medication
B. B.					12	M	47	4 weeks	39.0	43.0	Palpitation after previous thyroid medication
P. K.					13	F	25	5 weeks	40.0	42.5	Neurosis. Over-indulgence
T. F.					14	M	20	6 weeks	37.5	39.5	Over-indulgence. Tachycardia
B. L.					15	F	42	4 weeks	39.0	41.5	Menopause. Psychoneurosis. Over indulgence
H. F.					16	M	38	6 weeks	41.5	40.0	Hypertension. Headache after thyroid medication
D. O.					17	F	27	7 weeks	37.5	42.0	Palpitation after previous thyroid medication
F. S.					18	F	26	4 weeks	38.0	39.5	Over-indulgence. Neurosis
C. R.					19	M	36	6 weeks	37.0	38.5	Asthenia
M. A.					20	F	47	5 weeks	40.0	42.5	Hypertension. Tachycardia. Menopause

SUMMARY

The drug, d-Desoxyephedrine, a dextroanalogue of amphetamine, was administered to 20 obese patients.

In none of the cases did there develop an adverse effect upon the liver as determined by the estimation of the prothrombin time of the whole and diluted (12.5 per cent) plasma.

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An Appraisal of the Value of Diagnostic Biliary Drainage

By
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NEW YORK, N. Y.

IN 1923 the writer (1) presented for discussion the Meltzer-Lyon method of biliary drainage. The subject matter was then in a truly evolutionary phase. Only a brief period of six years had elapsed since its inception by the late Dr. Meltzer and his reference to it in a note in the Amer. Jour. of Med. Sciences in 1917 and the elaboration therefrom by Lyon into a simple, precise and highly scientific method which seemed to the writer to offer great promise in the diagnosis of hepato-biliary disease. Use of this procedure was predicated on the physiologic concept of contrary or crossed innervation. The writer well remembers the acrimonious remarks the subject aroused and yet, a method was presented which gave dependable physical access for a close study of the bile, on a par with all accessible systems whose secretory and excretory outputs were

available in the diagnosis of disease, not to replace but to supplement other laboratory aids in the pathogenesis of hepato-biliary dysfunction.

After five years of experience with drainage of the gall duct tract, the writer published his findings in 1929 (2), and although this inspired a less caustic discussion, it was sufficiently jarring to be vivid at this writing. After sixteen more years in which the writer has refused to abandon this onerous procedure, my feeling is much as in earlier years, that, the adverse criticism of some of my colleagues whose results have not equalled expectations, has not a little to do with an inadequate technique. A faulty procedure leads directly to erroneous interpretation of findings or to simple rejection of the practice. And, despite the continued success of other advocates of the procedure, it is not very avidly practiced, and what is more lamentable, its use by many is half-hearted and somewhat cynical. As to those practitioners who at one time undertook the method as an aid in diagnosis in hepato-biliary aberrations and later abandoned it, the author feels — following

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many a close interrogation — that this was the result of a failure to understand its intrinsic worth, which developed, by subconscious mutation, into an attitude of belittling its diagnostic import. It is a process of a simple mental transformation of the concept, "It is difficult" into, "I am not interested," and thence, "it is no good." I presume we are all familiar to a degree with this type of mental cowardice. But the technical difficulties are not insurmountable, and to facilitate the procedure of drainage from a mechanical angle the writer offered a Contrivance (3). It is of great aid and its use is recommendable.

The material for this paper was taken mainly from private practice wherein the writer's interest operated and obtained the values of the procedure through overcoming the hardships in the technique. For the purpose of clarification the author offers a synopsis he utilized at the Seventh Annual Graduate Fortnight of the New York Academy of Medicine. *This may provide guidance for the young reader in current literature and may help to reverse the disappointing attitude of some who shun the procedure, and of those who have recourse to it but half-heartedly.*

TRANSDUODENAL GALL-BLADDER DRAINAGE -SYNOPSIS

1. The history of gall duct drainage.
 2. Meltzer's law and the theory of crossed innervation. Analogy between the biliary tract and the renal system.
 3. Technic.
 1. Type of tube.
 2. Preparation of patient.
 3. Tests to determine successful egress of the tube through the pylorus.
 4. Films demonstrating various happenings of non-successful egress through the pylorus.
 5. Common technical faults.
 6. Selection of proper stimulants. Ineffectiveness of oral administration of stimulants.
 7. Segregation of bile into A.B.C. fractions. Significance.
 4. Methods of drainage Aspiration, gravity.
 5. Diagnostic Biliary Drainage.
 - Macroscopy.
 - Viscosity.
 - Interpretation of occult blood positive.
 - Microscopy, bile centrifuged.
 - Biliary drainage as a liver function test.
 - Biliary drainage as a differential test between surgical and Medical icterus.
 - Cystic duct catarrh.
 - Lambilla duodenalis.
 - Biliary migraine.
 - Gall-bladder diabetes.
 6. The significance of failure to recover B. bile. Failure to obtain any kind of bile, significance.
 7. Drainage preceding cholecystography, advantages.
 8. Surgical drainage versus medical.
 9. Therapeutic Biliary Drainage.
 1. Continuous.
 2. Intermittent.
 3. Transduodenal Enema. Object?
 - Indications —
 - Prevention of post-operative duct dilatation and to combat residual infection.
 - Post-typhoid (Biliary Migraine
 - Recurrent Influenza (Inertia of the gall bladder
 - Recurrent Tonsillitis (Biliary stasis
 - Catarrhal Jaundice (Gall bladder dyspepsia
- conductive to

Remarks: In selecting cases for biliary drainage the writer consulted the case histories. Believing that an adequate history is an instrument of precision he used a questionnaire captioned "The Gall-bladder Sheet" (4). It is the history which generally supplies the working hypothesis in the light of which laboratory findings assume a definite meaning. No doubt such "sheets" have been suggested before and can be found in medical literature. I believe, however, that they are not in general use; and their usefulness is to be emphasized. This form was not intended as a substitute for original thinking; it is offered merely as a handy guide to vital points requiring interpretation. Not many patients volunteer nutritional information arising from ingestion of certain articles of food; this must be ferreted out and assessed so that the cases for drainage may be properly selected. Information about the patient's gastric motility is a prerequisite to a successful drainage. Gastric peristalsis, gastric tone, and most important, the state of the pylorus, are essentials in gastric clearance. A play of spastic phenomena in the pyloro-duodenal theater often prevents successful egress of the duodenal tube from the stomach into the second portion of the duodenum. Knotting of the duodenal tube through gastric hyperperistalsis is a frequent cause for an unsuccessful test. A case (5) illustrating the importance of the use of the fluoroscope as the means, par excellence, for ascertaining whether the tube successfully passed through the pylorus, was published by the writer in 1924. The injection of a stimulant, $MgSO_4$, or olive oil before ascertaining with reasonable accuracy that the duodenal tube is out of the stomach is a likely cause for embarrassing the procedure. Microscopy of the biliary aspirates must be done immediately to avoid digestion of cellular evidence of pathology. Immediate cultural study is urgent to prevent less hardy organisms from being overgrown with the more rapidly growing groups. It is important to note that the concentration of the constituents of the bile is a variant phenomenon because it is influenced by a number of factors. The most essential is the part of the intra- and extra-hepatic gall duct system the bile comes from. Careful segmentation of the aspirates into A .B C. fractions is therefore important. The concentrating activity of the gall-bladder so changes the physical characteristics of the bile from that coming from the hepatic ducts that its identification is easy, informative and diagnostically instructive. Segmentation of bile into these fractions constitutes a normal sequence. When floccules appear in the observation window they can be promptly secured for microscopic search. Cholesterol chemistry and calcium bilirubinate pigment constitute pathognomonic evidence of gall duct disease. When there are bile stained degenerated epithelia, leucocytes, pus cells, a diagnosis of exfoliative cholecystitis merits consideration. Cystic duct catarrh does not give a characteristic symptomatology but offers convincing microscopy in biliary aspirates. Clinical material to illustrate this point is offered by a case of cystic duct obstruction with roentgen evidence of non-visuali-

zation of the gallbladder; by means of repeated biliary drainages, a normal cholecystogram was obtained. It is not a point of view but one of fact that biliary drainage preceding cholecystography facilitates interpretation of the cholecystogram and enhances its value. The viscus is filled with fresh bile, which entering laden with the dye, will give a sharper contrast than can be offered by stale or static bile.

When the clinical picture of a cholecystopathy is compelling and the cholecystogram reveals no departure from the normal, biliary drainage holds potential diagnostic criteria of disease. In support of this contention Bockus, in the third volume of his *Gastro-Enterology* writes "In all patients suspected of having cholecystic disease which cannot be proved by cholecystography, biliary drainage should be performed." In cholesterosis the symptomatology may even simulate that of cholelithiasis with the roentgen criteria of abnormality entirely lacking. Under such circumstances drainage is convincingly informative. If cholesterol crystals are found in B bile, cholesterosis may be held accountable for the symptoms.

The writer's two cases (6) of *Lamblia* associated with cholecystitis and simulating cholelithiasis may be cited as clinical material illustrating the intrinsic worth of diagnostic biliary drainage. One patient had twice been investigated roentgenologically with a diagnosis of non-visualization of the viscus, and surgical intervention was urgently advised. The second patient was intensely jaundiced. In both these cases the biliary syphonates revealed numerous actively motile flagellates protozoa in strands of mucus, identified as *Lamblia intestinalis*. It became apparent that there is no specific symptomatology of *Lamblia* infection other than mimicry and that this tropical protozoon may also be found in temperate zones.

THERAPEUTIC BILIARY DRAINAGE

It is important to bear in mind that there are five avenues for infection of the gallbladder; they are, portal blood, systemic blood, lymphatic circulation, ascending infection from the duodenum and direct peritoneal contact through adhesions from inflamed neighborhood viscera. A cultural study is, therefore, a path finder, a synergistic aid indicating the route to be taken for discovery of the underlying malady, when other clues are obscured. Detection of a microorganism sets us on the right search and inquiry. In advocating an admittedly onerous procedure, it is important to stress the principle upon which therapy is based. Meltzer pointedly wrote: "Bile stasis is of primary importance as a pathogenic factor in biliary disease." In the triad etiology of hepatobiliary disorders — disturbed metabolism, foci of infection and biliary stasis — the third component plays a dominant role. Stasis in itself may be conducive to an inflammatory environment of the mucus membrane of the biliary system and thus, two factors — stasis and inflammation — operate in the genesis of biliary calculi. It becomes apparent that, while the gallbladder normally acting as a reservoir does not give rise to pathological phenomena, when biliary-entero circulation is unduly delayed, stasis

serves as pathogenic element. As Meltzer wrote, "... may not conditions happen which are capable of converting the periodically occurring physiological quiescence of the gallbladder into abnormally prolonged quiescence and thus converting physiologic storage of the bile into pathological stasis?" This is the central point upon which pivots the value of therapeutic drainage, from a preventive as well as from a curative angle. Antagonistic activities occur in the gallbladder comparable to those which operate in the mechanism of the urinary bladder, and, a disturbance of the law of contrary innervation furnishes a pathogenic factor converting the physiological storage of bile into pathological stasis. A careful perusal of the original article by Meltzer (7) offers persuasive arguments in behalf of this therapy.

At the outset may I say that all cases of cholelithiasis, without surgical contraindications, are primarily surgical. The following figures merit consideration: Kaufman (8) states that "Gall stones are found in 86 per cent of cases of gallbladder carcinoma." There is therefore justification in assuming cholelithiasis as a chronic irritant with implications analogous to those in other regions in which chronic irritation is present. A study of the pre-calculus phase is the essential point in preventing non-reversible pathology.

A survey of the author's case records shows that, owing to careful selecting, but few conditions were subjected to biliary drainage for alleviation of symptoms. They were cases of acalculous cholecystitis with stasis roentgenologically confirmed, cases of non-occlusive jaundice, or only partly obstructive, infectious cholecystitis and atrophic arthritis. The latter were attended with hypochlorhydria. Some patients reported clinical response to HCl therapy synergised by a course of biliary drainage. Admittedly, to draw a conclusion from a meager series of cases is not prudent clinical medicine. My records show, however, that some of these patients called for continuous drainage. Amelioration in symptoms was stressed in the cases attended with marked icterus and pruritus, these were cases of partially occlusive icterus. In the cases of rheumatoid arthritis, the sequence in biliary aspirates was normal, but flocculation and cellular evidence of a diseased mucosa was detected. Despite the weight of evidence of relationship between the biliary system and arthritis, suggesting efficacious treatment as confirmatory of the diagnosis, it must be borne in mind that an apparent *propter hoc*, may in some instances be only a *post hoc* and that further search would have revealed a different offender. The ease felt in the involved joints was emphasized by some of the patients. This, of course, is in contrast with reported cases of the favorable influence of jaundice on arthritic patients. A worsening of the arthritis rather than amelioration would be the clinical expectation. From clinical observation and review of case histories of post-cholecystectomies and notes made of the interspersion of arthritic symptoms and the symptoms which seriously indicted the gallbladder and led to surgical eradication, the conclusion is warranted that in these

cases the infected gallbladder harbors a primary focus, and it is reasonable to believe that patients with joint complaints, invariably referred to as "rheumatism in the joints," enjoyed relief in this regard. I believe it wise not to reject out of hand the opinion of some workers that a diseased viscus can act as a focus and betray its presence in arthritic conditions. However, the gallbladder need not be the primary focus as in the case of streptococcus viridans descending into it from a remote region or of an ascending infection from duodenitis. In cases where vagueness dominated the clinical picture, without a history of biliary colic, with negative physical findings, particularly where symptoms, however vague, directed attention to systems external to the biliary system, and which were ignored by other clinicians, the writer resorted to speculative biliary drainage and was rewarded in many cases. We are all familiar with a large group of cases with overt symptoms of angina pectoris obscuring entirely the real enemy lurking behind the right subcostal arch. In chronic cases one often encounters a maximum pathology and a minimum symptomatology. It is this phenomenon that accounts for the cases of atypical cholecystopathy.

In the search for residual pathology in post-cholecystectomy syndromes, gall duct drainage might be rewarded with gratifying information. A viscid bile, and increased specific gravity, imply concentration, concentration in turn signifying common bile duct dilatation. Coffey (9) questions: "Is such dilatation harmless?" He cites two cases cholecystectomized because of gallstones and reoperated upon because of symptoms, one case about 18 months post-operatively, and one case 19 years after the operation. In both the common ducts were three-fourths of an inch in diameter. He writes: "We have a duct almost as large as a duodenum with an opening that is half as large as the duodenum itself." He further writes, "it is possible, of course, that even such extensive dilatation of the ducts as is shown in these cases may do no harm, but such conditions cause one to think. I am sure we would all prefer not to have such a duct." It is a proper assumption that a dilated duct would operate disadvantageously as would a small gallbladder.

In final analysis, we as clinicians are interested in substituting the obvious for the vague. In the procedure under discussion, we have a classic example of accessibility to the hepato-biliary apparatus. It is the window which accords a chance to look into the pre- and post-cholecystectomy syndromes. Like the first robin in early spring or the first frost in fall,

biliary drainage aids us in discerning a change, if there is a deviation from a normal sequence. By way of comparison; the urinary bladder is interpolated between the ureter and urethra, the gallbladder interposed between parts of the intra- and extra-hepatic gall duct system. They differ in modus of innervation, but alike they offer accessibility to their contents. In search for the cause of azotemia, one surely does not neglect examination of the urine. The same approach is applicable to the gallbladder. It is not within the scope of this paper to go into classification of jaundice, but suffice it to say that, if the question is, is a case of jaundice occlusive in etiology or is it the result of damaged liver parenchyma, the effort of obtaining bile for clinical study is well rewarded. A determination of the serum phosphatase activity as an indication of an occlusive icterus, if there is an increase, is not dependable. It has been ascertained that in intrahepatic pathology with cellular damage, the level of the enzyme activity rises without necessarily producing jaundice. In the presence of jaundice a high serum phosphatase does not single out an obstructive cause, since hepatocellular jaundice might be a sequence of a primary obstructive jaundice, with inundation of the liver cells with bile, separating them from their blood supply, causing cell necrosis, thus presenting an instance of both obstructive and toxic jaundice. Under such circumstances, the cephalin cholesterol flocculation test might parallel a high phosphatase enzyme activity as evidence that a damaged liver parenchyma has released the enzyme into the blood stream. The limitations of these tests could be at least partially compensated by combining tests. Since we can turn to an objective study of bile, the test is not competitive, but when sensibly employed offers complementary aid in differential diagnosis. It is interesting to note, that not infrequently, the clinician is intent upon finding a single disease, and when found he is then least likely to think in terms of concomitancy. Right upper abdominal disease with referred symptoms elsewhere is a striking example. If the patient has pain in the precordium, with a silent right upper abdominal quadrant, one must think of eliminating a right upper abdominal lesion with referred pain to the precordium. We may here point to Blumer's dictum, "Where there is an apparent conflict between the subjective and objective symptoms, the objective have greater weight in pointing to the diagnosis." Reverting to cholesterosis, the positive biliary findings in contrast with a normal Graham test is an instance of objective superiority and concerting with the clinical picture.

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Editorial

SOME NOTES ON PROCTOLOGY

PROCTOLOGY is a recently established specialty but it has already demonstrated its usefulness and value and has taken an accepted place in the circle of the medical specialties. New concepts and techniques have been developed which should be of interest to this group.

Concerning Proctosigmoidoscopy: "Without a diagnosis there can be no intelligent treatment." Too often the patient with rectal bleeding, protrusion, itching, pain, or a change of bowel habit is advised without an adequate examination. Hemorrhoids are present in about seventy per cent of patients who have rectal cancers, and in about forty per cent of these the surgeon operates to cure the piles and misses the cancer. The value of thorough investigation of patients exhibiting symptoms referable to the lower intestinal tract is well illustrated by the experience of Estes. In a period of eighteen months, simply by subjecting these patients to exhaustive examinations, he was able to raise his resectability rate from 45 to 85 per cent. Nature was particularly kind in fashioning the lower end of the digestive tract. It can be examined under direct vision for a distance of 25 centimeters in practically all cases and not infrequently it is possible to visualize the bowel to a much higher level. This can be done without inconvenience or discomfort to the patient. The risk of this procedure in expert hands is negligible. Furthermore, there is no other satisfactory way in which to examine this important area. The roentgenologists freely admit that the lower sigmoid, recto-sigmoid, and rectum are, for the most part, "blind areas." The sigmoidoscope will uncover the lesions which occur in this area. Indeed, after the lesion has been discovered, accurate observation will greatly facilitate arrival at decisions regarding operability, prognosis, and specificity of the disease process. As this procedure is resorted to more frequently it will become necessary to open the abdomen less often in order to arrive at an accurate diagnosis. Indeed, exploratory laparotomy may disclose only an inflammatory mass while the sigmoidoscope can reveal a carcinoma, diverticulitis, possibly even endometriosis. Finally proctosigmoidoscopy has been found to be of great value following surgery. When the site of anastomosis, excision, or inflammation can be seen, observation as to spur formation, lumen size, local recurrence, etc., may be very helpful.

Concerning Polyps: Adenomas of the colon and rectum are much more frequent in occurrence than is commonly believed. In one large series reported they occurred once in every thirty-five patients proctoscoped because of bowel dysfunction. Feyrter reported 1100 polyps in 1800 consecutive autopsies. At Lahey Clinic when fifty top executives at a bank were

examined routinely, four polyps were discovered in the first 21 of these men. Polyps are found at all periods of life, but the average age is 50. Today more than one fourth of our total population is over 45 years of age. Sixty per cent of patients with polyps are males. A study of the etiology of polyps is interesting. Twenty-five per cent of patients having chronic ulcerative colitis develop pseudopolyps as a result of inflammatory hyperplasia. Of these, ten per cent die of carcinoma. Other chronic inflammatory diseases of the bowel may produce like figures. Of the solitary polyps, ninety per cent are malignant. In a study of resected specimens of the large bowel, polyps were found in the vicinity of carcinomas in ten per cent. Congenital polyposis and polypoidosis are frequently familial. An estimated fifty per cent of these persons die of cancer which frequently manifests itself at an early age. More than one-half of all colonic cancers and polyps are within easy reach of the sigmoidoscope. As to gross types, polyps are sessile or pedunculated. Operability approaches 100 per cent. Histologically practically all are reportable as "low grade one (Broders) adenocarcinoma in adenoma." Rarely higher degrees of dedifferentiation are seen. Most pathologists will agree that if these patients live long enough they will die of carcinoma. Bleeding is the most common symptom produced although instances of obstruction, localized hyperirritability, intussusception and appearance of the polyps at the anal orifice have been noted. About fifty per cent of polyps are silent as far as symptoms are concerned. The average polyp seen on proctoscopy is almost a centimeter in size. Treatment consists of destruction of the lesion. The safest and easiest way in which to accomplish this is with the fulgurating spark. Obvious dangers in doing this are hemorrhage, perforation, and serosal irritation. These complications are very unusual. Anaesthesia is both unnecessary and dangerous in this procedure and consequently it is most often accomplished as an office procedure. In multiple polyposis when the entire colon is involved fulguration of all accessible polyps may be a very feasible procedure which can be followed by ileocolostomy and colectomy to spare the patient a permanent ileostomy.

Concerning Hemorrhoids: These are simply varicosities occurring superficially beneath the lower rectal mucosa and the perianal skin. The incidence, etiology, symptoms and signs of hemorrhoids are common knowledge. In addition to digital and visual examination of these patients it is most helpful to determine the extent of the deformity by observing the condition while the patient is straining at stool. This is probably the most accurate way in which to determine just how much surgery will be necessary to relieve the difficulty. In common with the other vascular enlargements found elsewhere in the body (excluding a few of those which are of the so-called "end vessel" type), these varicosities only, very rarely

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respond permanently to sclerotherapy. The vessels will recanalize in a short time. The anchoring action produced on the mucosa by chemical inflammation followed by fibrosis is likewise transitory since the inelastic scar tissue becomes markedly less extensive and quite elastic with the passage of time. It cannot be argued that the injection treatment of hemorrhoids is not dramatic, but it must be distinctly classified as a palliative procedure not unfraught with dangers and complications. Complications resulting from the injection treatment of hemorrhoids are too frequent in occurrence to undertake this therapeutic measure lightly. Commonest complications are sloughing and abscess formation. Fistula formation, hemorrhage, pain and incontinence, deformity and scarring also occur not infrequently. These are but a few of the difficulties seen. A more formidable list has been compiled by Doctor Samuel G. Gant. The various-sized submucosal indurations found following injection treatment are not grossly distinguishable from other lesions in most instances. Consequently, in the presence of doubt as to their etiology, the fastidious and reliable proctologist will demand that they be excised for microscopic examination. In a large series of submucosal indurations thus examined a substantial percentage were reported by the pathologist to be malignant. With all these objections to this type of treatment there is still another objection of tremendous significance. It is the fact that this seemingly simple, easy procedure, has insidiously lulled many practitioners into being content with in-

efficient, incomplete examinations. Consequently many serious lesions existing just a little higher up than the hemorrhoidal area are being missed. There is, of course, a place for this type of treatment in our armamentarium. In selected cases it may be used on elderly patients or on those who are for some reason unfit subjects for anaesthesia. It can be used in cases having small uncomplicated internal hemorrhoids. External hemorrhoids are not suitable for this type of therapy and in the presence of inflammatory conditions and scarring it is extremely dangerous. Since most persons who have hemorrhoids fall into the middle age group and have years of useful life ahead of them, surgery is the treatment of choice. Whichever of the described methods of hemorrhoidectomy is used should be adequate if the varicosities are eliminated along with any existing redundancy and the mucosa reanchored at its normal position at the internal border of the external anal sphincter. An ample, smooth anal outlet which will heal quickly with the minimum of scarring is the object of surgery. As in all dirty surgery, provision for drainage is of utmost importance. Post operatively, cleanliness is of prime importance for good healing as well as for the comfort of the patient. It is to be hoped that the barbecuing soldering iron and torturing "whistle" have been relegated — accompanied by the old routine post operative orders for mineral oil — to the archaic limbo where they properly belong.

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Book Reviews

The Chemical Composition of Foods. By R. A. McCance and E. M. Widdowson, Pp. 156, (\$3.75). Chemical Publishing Co., Brooklyn, N. Y., 1947.

This volume represents an unbelievable amount of analytical work as applied to foods commonly eaten and has been carried on, with few interruptions, by its authors for over 30 years. Protein, fat, carbohydrate, acid-base balance, calories and minerals all are estimated by gravimetric analysis and recorded. The book is unreservedly recommended to those requiring the contained information. Approximately 1,000 different foods are analyzed.

Paravertebral Block. By Felix Mandl, Pp. 330, (\$6.50). Grune and Stratton, New York, 1947.

Although the author lost many of his valuable case records (extending from 1922 to 1938) during the war, at Vienna, he has carried on his work since 1938 in Jerusalem and in this volume he gives an extensive account of paravertebral block, its technique and its application especially to diagnosis and the treatment of pain. In this connection the section on angina pectoris is particularly valuable. The volume carries a foreword by Dr. Max Thorek, and can be highly recommended.

The Diagnosis and Treatment of Diarrheal Diseases. By William Z. Fradkin, A.B., M.D., Pp. 254, (\$6.00). Grune and Stratton, New York, 1947.

This able work, which carries a foreword by But-

rill B. Crohn, deals succinctly yet extensively with all known forms of diarrhea, both from the clinical and laboratory points of view. Roentgenological studies are presented and illustrated by film reproductions. The newer work on regional ileitis, ulcerative colitis and psychogenic diarrhea is thoroughly considered. The book is useful chiefly because it brings together in one place just about all that it is necessary for anyone to know, be he a specialist or general practitioner, with respect to the diagnosis, prognosis and treatment of diarrheal disease.

Advances in Pediatrics, Vol. 2. Edited by S. Z. Levine, A. M. Butler, L. E. Holt, Jr., and A. A. Wecch. Pp. 409. (\$6.75). Interscience Publishers, Inc., New York, 1947.

This excellent volume presents 11 important subjects of topical importance relating to diseases of children, among which may be noted, virus diarrhea, atypical pneumonia, growth problems, rheumatic fever, purulent meningitis, acute infectious lymphocytosis and others. The character of the contributors assures the reader of authoritative opinions. For those pediatricists who seek condensed information on subjects of recent advance, this volume, which follows the plan of "Advances in Internal Medicine," is highly recommended. It is more profitable to deal with eleven subjects fully than to offer skeleton notes on a thousand topics, for the former method gives one the "feel" of the specialty and the attitude of leading clinicians.

Advances in Internal Medicine, Vol. 2. Edited by William Dack, M.D., and I. Snapper, M.D., (\$9.50).

Interscience Publishers, Inc., New York, 1947.

With a distinguished list of associate editors including Longcope, Minot and Keefer, and an equally distinguished list of 19 contributors, here appear 13 sterling articles dealing with the ventricular complex of the cardiogram, venous catheterization, angiocardiology and angiography, surgical treatment of hypertension, surgical treatment of tumors and chronic inflammation of the lungs, insecticides, aviation medicine, penicillin in subacute bacterial endocarditis and other infections, the rhesus antigen, pernicious anemia and megaloblastic anemias, nutrition in disease, and nutritional diseases in the Orient. Each topic, for one reason or another, is "hot" and in the foreground of current medical interest and each is written by an authority. This is a book very much to be desired. Davidson and Davis' article is probably the most lucid review to date on megaloblastic anemias, including the Addisonian complex.

Dermatological Clues to Internal Diseases. By Howard T. Behrman, M.D., Pp. 165, (\$5.00). Grune and Stratton, New York, 1947.

Approximately 400 diseases having definite dermatological manifestations are briefly described and, in about one-half the cases, the skin lesions are illustrated by half-tone engravings. The author has been particularly happy in his collection of photographs partly because they are technically excellent as pictures and all, without exception, dramatically reveal the characteristic lesion in such a way as to impress the disease on the mind of the physician. The book should prove of great value to the internist and general practitioner.

Abstracts Of Current Literature

(Microfilm copies of papers may be obtained from the Microfilm Service of the Army Medical Library at 25c per each complete article, not exceeding 25 pages in length—and 10c for each additional 10 pages or fraction thereof. Prepayment is not requested. Remittances may be made with subsequent orders and in such manner as found most convenient. Address—Microfilm Service, Army Medical Library, Washington, D. C.)

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CLINICAL MEDICINE

LIVER AND GALLBLADDER

Ivy, A. C., M. D.: *Motor dysfunction of the biliary tract.* (Caldwell Lecture 1946). (Am. J. Roentgen. and Radium Therapy).

It has been established that the sphincter choledochus or choledochoduodenal mechanism can contract in man with sufficient force to prevent the evacuation of the contracting gallbladder and to counteract the secretory pressure of bile. Convincing evidence is available showing that pain may arise (1) from the rather sudden distention of the biliary passages by a force within the range of the contractile power of the gallbladder and

the secretory pressure of bile, and (2) from a spasm of the sphincter choledochus and or the adjacent duodenum. There is adequate evidence of a physiological nature, provided by a large group of investigators, to justify the view that a motor dysfunction of the biliary passages may produce symptoms, or that such an entity as biliary dyskinesia exists.

In the absence of manometric studies via a choledochostomy the clinical diagnosis of biliary dyskinesia is difficult, if not impossible to prove. The strongest circumstantial evidence in support of the diagnosis in the presence of a gallbladder which visualizes is the visualization of the hepatic ducts with pain after the ingestion of a fatty meal. This combination has only

rarely been observed. The diagnosis of biliary dyskinesia in the patient with or without a gallbladder is a challenging roentgenological and clinical problem. There is reason to hope that the isolation and use of cholecystokinin will assist in the solution of the problem.

REHRUSS, M. E.: *Evolution of gallbladder disease.* (Rev. Gastroenterology, April 1947, 14, 4, 227-236).

The author points out that the general study of gallbladder disease has crystallized along three lines, namely infective, chemical and metabolic disturbances and finally stasis. He reviews his own work on experimental infection of the gallbladder in animals, in which the most common etiological factor was a non-hemolytic streptococcus, although about half a dozen other organisms are capable of producing the same changes in the organ. The streptococcus concerned was morphologically similar to the *streptococcus fecalis* and it is hard to estimate when a carrier becomes a serious offense. Toxins, viruses, nonbacterial agents and even allergic phenomena may indeed injure the gallbladder, though this is difficult to prove. Fibrosis and degeneration of the muscular wall of the gallbladder is one of the chief pathological findings. We might be able to study pure bile if cholecystokinin becomes available for clinical testing. The new antibiotic agents raise our hope for better results in treating the disease.

TUMEN, H. J., MONAGHAN, J. F., AND JOBB, E.: *Hepatic cirrhosis as a complication of chronic ulcerative colitis.* (Ann. Int. Med., April 1947, 26, 4, 542-553).

In five cases of cirrhosis of liver encountered among 151 patients suffering from ulcerative colitis, suspicion of the condition was usually aroused by clinical evidence, though once by abnormal responses to hepatic function tests. In 4 cases the diagnosis was confirmed by peritoneoscopy, a procedure which proved safe and was well-tolerated by these patients. In one case alcoholism and dietary deficiency may have played the chief etiological role, but in 4 the cirrhosis seemed to have been caused by the colitis. Hypoalbuminemia persisted in these patients despite efforts to restore the level of serum albumin, and this suggests that hepatic disease may be important in producing the hypoalbuminemia, so characteristic of persons with ulcerative colitis. The cirrhosis seen in these cases probably resulted from faulty absorption of proteins and vitamins as well as large amounts of protein lost in the rectal discharges.

GRIFFITH, W. H., M. S., Ph. D.: *Fatty infiltration and hepatic degeneration.* (Miss. Valley Med. J., April 1947, 69, 2, 64-67).

Fatty infiltration of the liver does not at once upset the liver metabolism because of the regenerative power of liver cells and the liver's high functional reserve. After pancreatectomy fatty degeneration of the liver

occurs, even when insulin is used, unless pancreas or its equivalent is included in the food. One of the effective components of pancreas is choline, a component of lecithin. Methionine is a valuable dietary precursor of choline and can replace dietary choline, and can protect against either protein or choline depletion. Dietary fat is not a prerequisite for the development of a fatty liver, but high fat diets aggravate the condition, and the same applies to cholesterol. The liver, we know today, has a high requirement of choline and of sulfur containing amino acids and possibly of inositol also. Diets low in protein and in essential nutrients impose unnecessary hazards on liver function.

GLENN, FRANK: *Chronic biliary tract disease.* (Rev. Gastroenterology, April 1947, 14, 4, 240-244).

The author believes that removal of the diseased gallbladder at an early stage is the best way of avoiding the serious complications, acute cholecystitis, common duct obstruction and liver damage, particularly today when the mortality of the operation is less than 3 per cent, especially in view of the fact that non-surgical therapy cannot, on the whole, recommend itself in view of the indifferent results obtained.

METABOLISM AND NUTRITION

SHOURIE, K. L.: *The nutrition problem in Punjab.* (Journ. of Indian Med. Assn., Dec. 1946, XVI, No. 3, pp. 82-95).

In the Punjab, there are only 1.07 acres of cultivated land per person which, judged by Stiebling and Ward's estimations, is incapable of producing even an "emergency restricted diet," i. e., a diet consisting largely of cereals and designed to tide unemployed persons over a short period of privation. Although the Punjab exports large amounts of wheat and some rice, millet and barley and is therefore known as the granary of India, its production of cereals per head of population has declined 33 per cent in the past 40 years, due to marked population increase. If the cattle and human requirements are figured, it is found that the Punjab is now a deficit province even in cereals and it is shown that a great lack of the protective foodstuffs also exists. Public health and hospital investigations show about 2 per cent incidence of phrynoderma, Bitot's spots and angular stomatitis. Considerable nutritional anemia also is present. The author suggests increasing leafy vegetables and milk and also improvements by means of conservative methods of cooking. He does not suggest birth control.

DEBRE, ROBERT: *Renal diabetes accompanied by rickets, hypophosphatemia and developmental anomalies in infants and children.* (Pediatria Danubiana, Jan. 1947, 1, 1, 8-15).

The characteristic symptoms of this syndrome are renal diabetes, anomalies in the development of the bone system, hypophosphatemia, acidosis and cystinuria. Fanconi, De Toni and Debre were the first to describe

this condition. There is an early form occurring in infancy and a late one observed at the age of 10 to 15 years. There is a trend to familial incidence and recessive heredity.

The infant suffering from the disease fails to develop and there is loss of appetite, constipation, and abundant fluid intake. Later on fever may ensue and last for a time. Simultaneously, craniotables with wide sutures, osteoporosis, and spontaneous fractures appear. There is glucosuria but the blood sugar level is normal. The rise of the sugar tolerance curve is sudden and goes well above the normal and the return to the fasting level is delayed. Adrenalin and insulin tolerance tests are normal. The alkalie reserve decreases in the blood. In the urine the amount of organic acids, such as lactic, acetic and beta-oxy-butyric acid is increased while acetone appears in traces only or may not be present at all. Of the amino acids especially cystine and tyrosine are excreted in large quantities, further ammonia and from time to time phosphates. The urine is alkaline or neutral. The serum phosphorus content is low, while that of calcium normal. In the sediment granulated casts and leucocytes can be seen. Failure of renal function is frequent. Death is due to acidotic coma and occasionally to azotaemia.

The late form is characterized by dwarfism, deformity of limbs, bone fragility and obesity of the waist and the hips. The change of the blood and urine are similar to those seen in the early form. Death occurs like in infants. Treatment is only symptomatic, alkalis can be given against the acidosis and big doses of vitamins D₂ and A against the phosphataemia.

The pathologic basis of the disease will be dealt with in another paper. The underlying cause is probably an alteration of the renal tubules and the deposition of cystine in the reticuloendothelial system and other organs.

KERPEL-FRONIUS, E.: *Dehydration by fluid deprivation* (Pediatria Danubia, Jan. 1947, 1, 1, 33-38).

Thirst causes of special type of dehydration. Analyses of the brain and muscle tissues indicate, as was shown by earlier balance experiments, that the loss of fluid is divided between the extra- and intracellular parts of the body. In consequence of this division of the total loss of body water between the two fluid components, plasma volume is conserved even in cases of extreme total water losses (up to 30 per cent of body weight). The loss of extracellular water is proportionally bigger than the loss of body chloride. In this type of dehydration no parallelism is found between salt and water. Hyperchloraemia and hypersodiumaemia are coexistent with excessive chloropenia.

PENNOCK, L. L.: *Clinical experiences with benadryl in allergic states*. (Pennsylvania Med. J., March 1947, 50, 6, 609-613).

The author found that benadryl and pyribenzamine

are valuable for the palliative treatment of allergic states, their efficacy depending upon their power to block the action of histamine at its site of action in the body. Benadryl produced relief in 91 to 100 per cent of acute cases and in 66 to 100 per cent of chronic cases. In seasonal hay fever, improvement varied from 59 to 95 per cent, which is as good as desensitization therapy. Perennial vasomotor rhinitis responded in 74 to 87 per cent. Most cases of bronchial asthma have not improved. Drowsiness is the most common side reaction of the two drugs, and occasionally they must be discontinued because of it.

LEVY, H.: *Folic Acid in Pernicious Anemia*. (Brit. Med. J., March 29, 1947, 412-413).

The examination of smears obtained from sternal puncture, at intervals up to 48 hours following the oral administration of a single dose of 50 mgm. of folic acid, showed a very similar disappearance of nucleated red blood cells to that found following a single injection of reticulogen. The author believes that repair in pernicious anemia is effected by newly produced cells of non-megaloblastic series, rather than by a sudden maturation of cells of a megaloblastic series.

KEYS, ANCEL: *Human fitness and the state of vitamin nutrition*. (Nutrition Rev., May 1947, 5, 5, 129-131).

Good nutrition is that condition which permits the highest state of fitness. However, better methods for evaluating fitness are needed, providing formidable problems. In vitamin deprivations, many symptoms appear long before physical and mental fitness are affected. The bulk of evidence indicates no gain in fitness of adults from vitamin supplementation added to a good American diet. Changes in physical fitness are neither early nor especially prominent results of diets extremely low in vitamin A. Subsistence on a diet very low in ascorbic acid eventually produces a decline in physical fitness but this does not seem to precede the more characteristic changes in the gums, capillary resistance and wound healing. With both vitamin A and C it is not proper, from present evidence, to suggest that low states of fitness may be ascribed, in the absence of other signs, to deficiencies in these vitamins. On diets in which the major B vitamins are reduced to 34 to 40 per cent of the National Research Council's Recommended Daily Allowances, elaborate and well controlled studies have failed to disclose any loss in physical or mental capacity within periods up to at least six months. Anorexia and mental depression occur early but are corrected by the provision of thiamin alone. Changes in fitness are preceded by one or more of the following—anorexia, personality changes, signs of polyneuritis, oral or cutaneous alterations, increased pyruvic acid in the blood. Vitamin supercharging confers no benefit in terms of fitness, and fitness is not peculiarly sensitive to vitamin deficiencies.

SCOTT, J. C. AND ROB, C. G.: *Traumatic Uremia; recovery.* (British Med. J., April 9, 1947, 529-530).

The authors describe a case in which a penetrating wound of the right thigh with division of the femoral artery and vein, without any apparent injury to the abdomen or left leg, led to ischemia of both legs. This was followed by a great increase of blood urea and other signs pointing to the onset of traumatic uremia. After splanchnic block, the blood urea fell and the general condition improved sufficiently to permit amputation of both legs, following which recovery was uninterrupted. The gangrene of the left leg was not explained.

BRANSBY, E. R. AND MAGEE, H. E.: *Rations and nutritional needs.* (Brit. Med. J., April 19, 1947, 525-528).

When bread rationing was introduced into England, it posed a problem for these individuals in a national society whose energy requirements were above the normal, due chiefly to large appetites. Previously, great flexibility existed in the national diet, because such individuals could supplement their rations by eating bread in sufficient quantities. Yet, notwithstanding the rationing of bread, the authors point out that there still exists considerable flexibility in the rationing system depriving from one or more of the following — (a) unrationed foods, (b) canteen, school or similar extra needs, (c) the use of "points" to the best advantage, including the exchange of points into bread units, and (d) diversion of rations from family members with small needs to others with greater needs (the family pool).

CONN, J. W.: *The diagnosis and management of spontaneous hypoglycemia.* (J. A. M. A., May 10, 1947, 134, 2, 130-137).

We should become conscious of this syndrome if we are to recognize the relatively large number of patients suffering from spontaneous hypoglycemia. Of the causes, there are three which cover about 90 per cent of all cases — (1) functional hyperinsulinism, (2) organic hyperinsulinism, (3) hepatogenic hypoglycemia. Functional hyperinsulinism can be controlled successfully by a high protein, low carbohydrate diet. Organic hyperinsulinism requires pancreatic surgery. A diet high in both carbohydrate and protein is indicated in hepatogenic hypoglycemia, also at times cholecystectomy. Hepatogenous hypoglycemia may be recognized by a tendency to low blood sugar levels and also by evidence of hepatic disease as revealed by liver function tests.

BROOKSBY, J. B.: *The serum proteins of the domestic animals.* (Proc. Roy Soc. Med., March 1947, XV, 50, 187-189).

Owing to the fact that varying techniques have been used (salting-out, electrophoresis, ultra-centrifugation)

and owing to considerable variation due to breed, age, sex and general condition of the animals examined, fairly wide variations occur in the estimates of albumin and globulin, as reported by various investigators. Electrophoresis gives much lower values for bovine serum albumin than obtained by "salting out" methods. If, as one author found, the gamma globulin fraction of bovine serum represents 38 per cent of the total protein, then concentration of antibodies from the gamma fraction, as in foot-and-mouth disease, is very poor.

SURGERY

TRINCA, A. J.: *The treatment of acute perforation in peptic ulcers.* (Med. Jour. Australia, Mar. 29, 1947, No. 3, 385-390).

This article is an intelligent plea, supported by extensive statistics, against the use of the drainage tube in the presence of diffuse peritonitis. In a large series of 568 operated cases, 29.7 per cent died when drainage was used, while the death rate was only 9.7 per cent in cases where drainage was not employed. He claims that the diffusely inflamed peritoneum actually cannot be drained, and that the use of drainage dehydrates the patients. Prolonged procedures for closing the perforation add greatly to the shock and the author merely covers the perforation securely with omentum. By observing these points, as well as giving due attention to pre-operative preparation, and the use of penicillin and sulfonamides post-operatively the mortality rate can be greatly reduced.

EXPERIMENTAL MEDICINE

SECRETION

TRETHEWIE, E. R., CLELAND, J. B. AND PENGELLY, T. J.: *Anticoagulant liberated from perfused mammalian liver.* (Med. Jour. Australia, Mar. 15, 1947, 1, 11, 321-323).

It is demonstrated that the anticoagulant effect of diluted blood perfused through the liver of the cat is due, either wholly or in part, to an output of a reddish substance which is precipitated by acetone from 3:1 chloroform-methanol and on taking up in Tyrode's solution forms an xanthochromic solution. It is probably a sphingomyelin. Protein may form a compound with the lipid.

MISCELLANEOUS

JHATAKIA, K. U. AND MANKAD, K. K.: *Incidence of protozoa and parasites in routine stool examinations.* (Jour. Indian Med. Assn., Nov. 1946, XVI, No. 2, 44-47).

Out of 856 routine stool examinations carried out in 1945 at Sheth Devkaran Muljee Pathology Department at the Sir Hurkisonadas Hospital, Bombay, 422 showed some parasitic or protozoal infestation while

434 were negative. Examination included that for protozoa, flagellates, ciliata, and helminths, and most of the castes of Indian society were represented, though Hindus predominated. *Entameba coli* was found most often (21.5 per cent) of all protozoa although *entameba histolytica* (13 per cent), *endolimax nana* and *iodameba butshili* also were found. Among the flagellates, *Giardia lamblia* greatly predominated in both the vegetative and cystic stages, but there were a few cases each of *Trichomonas hominis* and *Chilomastix mesnilli*. *Nematodis ascaris lumbricoides* led among the parasites with hook worm (*angylostoma*) a close second, and a few cases of whip worm, thread worm and strongyloids *stercorides*. Many stools showed mixed infestation. The majority of the patients were vegetarians, so *Tinea* infection was negligible. The authors feel that a stool examination is essential in all gastro-enterological cases.

NEAL, M. P., M. D.: *The diagnosis of pernicious anemia*. (Miss. Valley Med. J., April 1947, 69, 2, 53-58).

The author emphasizes the difficulties in diagnosis of Addisonian anemia, especially now that liver is given to all cases of anemia, and consequently the diagnostic features of the blood picture are altered prior to the examination. Neal divides a circle into 12 equal segments and in each places one of the twelve valuable signs and symptoms, so that each segment contains 8.33 per cent of the evidence and he feels that patients showing 66 per cent or more of these signs can be considered true cases of pernicious anemia, whereas those showing less than 40 per cent are doubtful. Study of this method indicates that he is probably correct.

CATHCART, J. P. S.: *The emotions in gastro-intestinal disturbances*. (Canad. M. A. J., 55:465, 1946).

"No other function of the body plays a greater part in the emotional life of a person from infancy on than does the taking of food . . . To the healthy and happy infant, feeding and loving are inseparable." Alexander divides his gastrointestinal cases of emotional origin into three groups: first, the largest group, patients with a range of symptoms from minor disturbances, such as epigastric distress, nausea, belching, heartburn, etc., to actual peptic ulcer. The second group has diarrhea as the predominant symptom, and the third, chronic constipation.

Alexander tries to understand the patient's emotional attitude to his environment in terms of three tendencies:

1. to receive or to take
2. to retain
3. to give

If the normal channels of emotional expression are blocked by inner conflicts, the gastrointestinal tract may be used instead, in the first group, in the conflict between deep-seated urges for dependency and the attempt to deny or reject them. Some identify this de-

pendency urge as maternal attachment, which is denied by the patient or frustrated by the circumstances. The maternal dependency theory may provide some explanation for the prevalence of gastrointestinal disturbances in males.

In the second group the same conflict is present, but it is expressed through painful evacuation, expressing an effort to make restitution and also aggressive, and even sadistic, tendencies.

The third group represents a rejection of an obligation to give, and is often associated with tendencies of thrift and even stinginess.

The author has given special study to the first group and has only a limited experience with the other two. He is in agreement with Alexander's views to a large extent in relation to the first group on the basis of his own studies, and is therefore inclined to give them prominence, also, for the other groups.

Peptic ulcer and conditions commonly referred to as "gastric neurosis" or "functional dyspepsia" are put in the same group by the author (stemming from similar psychic mechanisms). Going even further, a close kinship is claimed between peptic ulcer and the psychoneurosis — anxiety type. This was seen statistically in hospital admissions in the Canadian Army, where an amazing parallelism was found in the hospitalization incidence of peptic ulcer and anxiety neurosis. These observations may throw more light on the parallelism:

1. Frequently both entities are present in the same patient.

2. A family pattern of anxiety and tension may express itself in different members, sometimes as anxiety neurosis, and sometimes as peptic ulcer or some other variant. Every case study should therefore include inquiry into all those possibilities and their occurrence in the family history.

3. The author's psychological studies showed a certain interchangeability in the life histories of his peptic ulcer and anxiety neurosis patients. He believes that no case of peptic ulcer is being adequately treated ". . . without a study of the unhealthy emotional background."

4. Rubin and Bowman, in recent studies, found some indication for electroencephalographic and personality correlations between anxiety neurosis and peptic ulcer.

In ulcer cases there is a pronounced liability of the autonomic reflex in response to minor psychic stress. It is believed, therefore, that imposed cautions and restrictions tend to create their own somatic tensions, which might even outweigh the expected gains. The author and his associates often successfully removed restrictions, and put the patients on a full diet without medication, after first clearing up the conflict material. In the treatment of his cases, besides individual psychotherapy, apparently kept as superficial as possible, group therapy and reeducation also were used. It was found that psychotherapeutic methods of dealing with anxiety neurosis are equally effective in peptic ulcer.

(O. P.)

(Reprinted from *Psychosomatic Medicine*, IX, 2, 1947)

WINDHOLTZ, F.: *Problems of acquired radioresistance of cancer; Adaptation of tumor cells* (Radiology, April, 1947, 48-4, 398-403. The author analyzes the cause of acquired radio-resistance of malignant tumors on cellular basis.

The histologic and radiobiologic behavior of the mucous membrane of the larynx after irradiation may be used as a test experiment for radiobiologic conditions present in the irradiated cancer. Microscopic examination shows that cells of laryngeal epithelium are primarily destroyed by irradiation and that a new and more highly differentiated metaplastic epithelial structure develops after disintegration of the original mucous membrane. This newly developed epithelium possesses lower radiosensitivity. Its cells are characterized by (1) ability to regenerate under doses of irradiation which previously destroyed them; (2) a higher degree of differentiation; (3) a capacity to adapt their metabolism to the nutritive changes of the irradiated, subepithelial connective tissue. Thus the regenerated epithelium displays signs of increased radioresistance.

It is very likely that similar changes take place in the tumor itself. The radiant energy destroys primarily many of the tumor cells; however, a new strain of cells develops from structures which, in the nascent state, were exposed to the direct or indirect effects of irradiation. The new cell generations gradually become more highly differentiated. A change in their radiosensitivity occurs, corresponding to this new degree of differentiation and to the capacity of cellular adaptation to the nutritive properties of the adjacent simultaneously irradiated connective tissue. Tumor cells which are able to adapt themselves maintain their newly acquired properties in successive cell generations. Gradually the entire tumor becomes transformed into a growth, the radiobiological properties of which are adapted to the biological conditions prevailing during and after irradiation. In this new surrounding, the tumor either disintegrates or its radioresistance is increased. The decrease of radiosensitivity of most of the metastatic tumors, of tumors invading muscle, fat, cartilage, bones, etc., finds a natural explanation in their ability to adapt their metabolic and radiobiological properties to those of the new host tissue which is, as a rule, more radio-resistant. Anaplastic tumors, which are unable to produce more highly differentiated structures, remain sensitive and disintegrate, due to the direct effect of radiant energy, as long as they grow in their original matrix; however, as soon as they invade heterotopic tissues (displaying their capacity for adaptation), their radiosensitivity decreases. It seems reasonable to assume that "residual" tumors after irradiation, and recurrences of irradiated tumors, must be regarded from a radiobiological standpoint as metastases developing

in the bed of the primary tumor, for the growth occurs in a tissue modified to a variable extent by previous irradiation. This modified tumor bed may be considered structurally and radiobiologically as heterotopic tissue, thus explaining the loss of radiosensitivity of "residual" and recurrent tumors.

HALSTEAD, JAMES A.: *Functional gastrointestinal disorders: lessons learned from military medicine*. (New England J. Med., 235:747, 1946).

Functional gastrointestinal disorders, which constituted a large part of the disability from medical causes in the United States Army during the war, were found to be best treated, not by sedatives, diets, antispasmodics, rest, or hospitalization, but by dealing with personality disturbances directly and promptly. In patients with symptoms superficially resembling ulcer, 80 out of 100 studied were found to have psychoneurotic symptoms which rendered them unfit for military duty. Among the actual ulcer patients, only 6 per cent were rendered ineffective by psychoneurosis. The ulcer patient presented a restless, ambitious personality, with excessive self-reliance, and no tendency to make use of his symptoms to avoid duty. The patient with functional dyspepsia was submissive, passive and tended to use his symptoms in order to avoid unpleasant situations. Clinical symptoms of these two groups of patients are described. The above study was made on an overseas combat group, and results are contrasted both clinically and psychologically with patients seen in civilian practice. Four main explanations for functional gastrointestinal disorders are outlined: 1) primarily associated with organic disease, 2) excessive physiological strain, 3) low threshold for gastrointestinal symptoms, 4) emotional disturbance or neurosis. It is recommended that treatment be based upon whichever of the above causes is pertinent. Bed-rest, diet, and drugs, in the treatment of neurosis, unless used merely as temporary adjuncts to psychotherapy, are considered detrimental because of secondary gain. Delving deeply into the background of the patient was found unwise, in the military setting, but simple psychotherapy on the realistic level of being told what the trouble was, and that the patient would have to get used to it, was found effective. The diagnosis itself, of the functional disorder, was found very helpful to the patient's adjustment. Psychotherapy was found most difficult in the group with psychogenic symptoms, which constituted four-fifths of the soldier patients, and is estimated to be a large group in civilian practice also, as this type of patient resists seeing that his symptoms are based on emotional conflict, avoids psychiatric treatment but prefers physical treatment, and may have firmly fixed dependence upon medical rituals.

(M. L. M.)

(Reprinted from *Psychosomatic Medicine*, IX, 2, 1947)

Certification of Death of 1,000 Diabetic Patients

by
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and
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BOSTON, MASS.

THE EPIDEMIOLOGICAL PATTERN of diabetes has altered in recent years. This is evinced by changes in the mortality trends, in the morbidity rates, in the average age at time of death, and in the duration of the disease.

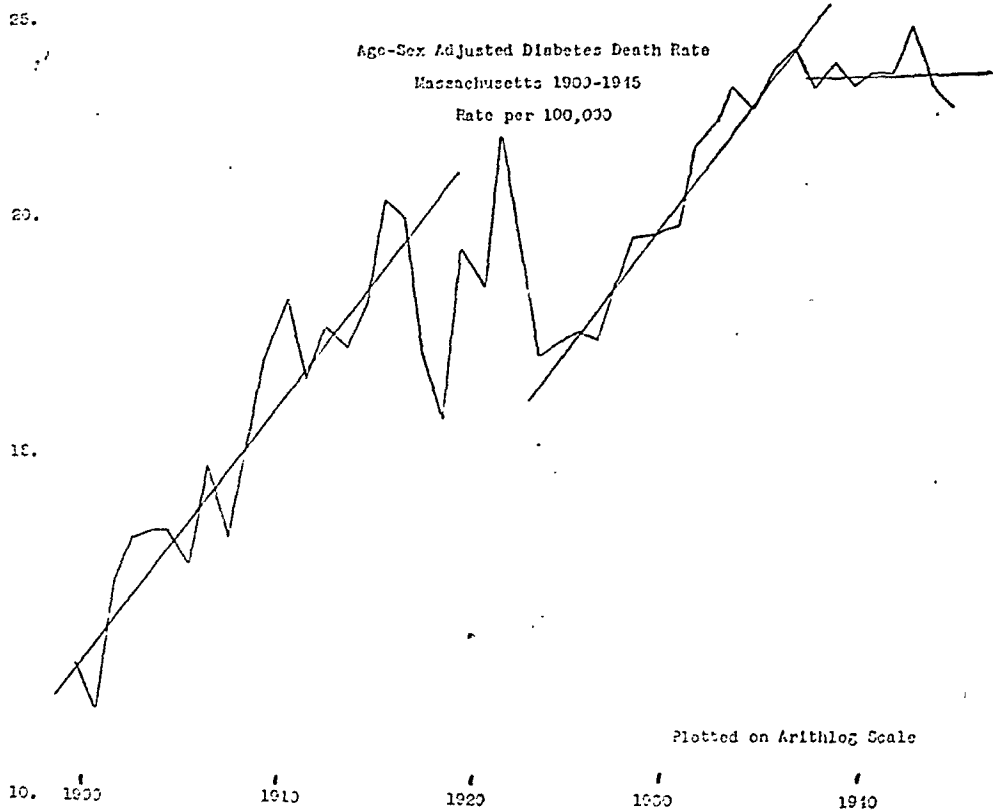
DIABETES MORTALITY IN MASSACHUSETTS

Trends

A straight line upward trend fits the crude rates for diabetes in Massachusetts from 1900-1917. In 1918 and 1919, coincidental with the influenza epidemic, there was a drop in the certified deaths from dia-

even steeper than that preceding the discovery of insulin.

When the diabetes rates were adjusted for age and sex, the trend computed from the logarithms of the rates was found to fit slightly better than a trend from the rates. From 1900-1917 there was a three per cent annual increase; from 1924-1937 a similar one; while from 1938-1945 there was no trend. The years 1918-1923 were omitted from these calculations as the abnormality of the rates in 1918 and 1919, occasioned by the influenza epidemic, and the sharp fall in the rates from 1922-1924 following the discovery of insulin, were sufficiently great as to disturb otherwise close-fitting



betes, followed by a resumption of the upward trend. It is interesting to note that insulin was first used in Massachusetts in August 1922, and that in 1923 and 1924 there was a drop from the trend line (1). This interlude was followed by an upward trend which persisted until recent years,

trends. The constants connected with these trends indicate that with the removal of the trends the variation is practically that of chance.

TABLE I

Average Annual Percentage Change in Diabetes Mortality

	Annual Percentage Increase	S.D.	σ β	σ π
1900-1917	3.13	2.6	.7	1.1
1924-1937	3.08	2.5	.7	1.0
1938-1945	— 0.05	0.7	.7	

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Submitted March 24, 1947.

Apparently for the past several years there has been no increase in the age-sex adjusted diabetes death rates in Massachusetts, and both the crude and adjusted rates for 1944 and 1945 suggest that a decrease may be occurring. In 1937 protamine zinc insulin became available (1). The introduction of this product made possible the administration of insulin at one time during the day, and as a result more people consented to use it. Inasmuch as following the introduction of the original insulin the trend in the death rates was altered for only a short period of time, it is problematical whether the change following 1938 could be explained wholly by the use of protamine zinc insulin.

Age at Time of Death

The mean age at time of death of diabetics increased from 52.0 in 1900 to 66.8 in 1945. While the mean age at death of diabetics increased 28 per cent in this period, that of individuals dying of cancer increased only 10 per cent.

It is presumed that the change in the age at death of those dying of cancer is due primarily to the changing age composition of the population. Inasmuch as both of these diseases attack individuals in similar age groups, to a large extent, it seems probable that the change in the mean age at time of death of diabetics depicts, in addition to the aging of the population, the gains made in the duration of life of individuals with the disease.

ONE THOUSAND DIABETES RECORDS
(JOSLIN'S)

A study based on Joslin's records of 372 individuals with diabetes who died in 1926-1928 and 372 individuals who died in 1931-1933 was reported ten years ago (2). These records were completed to determine the recorded cause of death. Similar data have been obtained from 494 individuals who died in 1936-1938 and from 506 individuals who died in 1941-1943.

Age at Onset

The mean age at onset of these cases has shown relatively slight change in the four periods. It is believed that the actual age at onset of the disease has not varied, with the exception of such variation as would be caused by the aging of the population.

Age at Time of Death

The mean age at death found in Joslin's cases differs somewhat from that of the classified death certificates in Massachusetts. In determining the mean age at death from the death certificates only those with diabetes recorded as a primary cause of death were used, while Joslin's records also included those on which diabetes was recorded as a contributory cause.

Cause of Death Classification

Individuals who die with diabetes fall into one of four groups:

- A. Those who die of the disease and are so classified.
- B. Those who die of intercurrent disease but are classified as dying of diabetes, according to the Joint Causes of Death Classification.
- C. Those who die of intercurrent disease and are classified as so dying, but with diabetes as a contributory cause.
- D. Those who die of intercurrent disease, and diabetes is omitted from the death records.

Individuals of the first two groups, A and B, are classified as dying of diabetes and so published in the vital statistics reports. Altshuler believes that from a clinical standpoint only group A should be considered as deaths from diabetes (3). This might be advantageous in certain types of research, but in studies dealing with the incidence of the disease records from all four classifications are necessary.

Approximately 64 per cent of individuals with diabetes were classified as dying of diabetes. Eleven per cent of individuals dying of diabetes were classified as dying of some other disease with diabetes a contributory cause, while 24 per cent of the certificates of individuals known to have had diabetes failed to have the word diabetes written on the death certificates.

Confirmation of the percentage of individuals classified on the death certificates as dying of diabetes has been obtained from Altshuler's study and a personal communication from Dr. Lester Palmer of Seattle, Washington (4). From Altshuler's data the rate was 65.3 ± 3.3 and from Palmer's, 69.1 ± 3.0 . These are both consistent with the authors' findings.

TABLE II
Death Record Classification of Individuals Dying with Diabetes

	1926-1928	1931-1933	1936-1938	1941-1943	Aver.
Total Diabetic Cases	372	372	494	506	
A. B. Classified as diabetes	60.0 \pm 2.5	65.9 \pm 2.4	68.1 \pm 2.1	63.2 \pm 2.1	64.3
C. The word diabetes appeared on the death certificate but classified otherwise.	12.1 \pm 1.7	14.0 \pm 1.8	7.9 \pm 1.2	11.7 \pm 1.4	11.4
D. Failed to have the word diabetes on the death certificate.	27.9 \pm 2.3	20.1 \pm 2.1	24.0 \pm 1.9	25.1 \pm 1.9	24.3
Age at onset	53.1	52.2	55.0	54.9	
Age at time of death	60.4	61.5	66.2	65.8	

Death Certificates With and Without the Word Diabetes

An effort was made to determine in what respect individuals whose death certificates included the diagnosis of diabetes differed from those whose certificates did not include it.

There was no difference between the individuals in these two categories in respect to age and sex.

There was no difference between the two groups in respect to the periods of observation by Joslin, nor was there any difference in regard to the interval of time that elapsed between the last visit to Joslin and death.

The percentage of individuals who were hospitalized at time of death showed no significant difference between the two groups.

The average duration of the disease was shorter among those not having diabetes mentioned on the death certificates, but the significance was borderline.

The two groups were compared to determine the occurrence of diseases other than diabetes on the death certificates. The two groups did not differ significantly regarding the occurrence of the following diseases on the death certificates: pneumonia, tuberculosis, intracranial lesions, heart disease and diseases of the genito-urinary tract. Arteriosclerosis showed a significantly greater prevalence in the group with diabetes mentioned on the death certificates while cancer and violent and accidental deaths were recorded more frequently on certificates on which diabetes was not mentioned. This is understandable, for physicians signing death certificates for accident cases and cancer might neglect to include diabetes and arteriosclerosis as contributory causes.

Of those having diabetes mentioned on the death certificates 20.7 per cent were recorded as either taking no insulin or taking it for only a short period of time; while of those not having diabetes on the death certificates 43.8 per cent were in this category. These percentages were significantly different. If individuals using little or no insulin can be assumed to have diabetes in a mild form, then this variable would be responsible for the omission of the word diabetes from many of the certificates.

Duration of Diabetes

In order to determine the durations between known symptoms and death, the data of the 1000 records of this study have been augmented by data from records of other years.

The average duration of the disease as obtained from Joslin's records is longer by about two years than the duration obtained for the same individuals from their death certificates. Joslin's records furnish a better picture of duration than do the death records, since Joslin's information regarding date of onset was elicited from the individuals themselves, and in most instances the date was established long before death. Further confirmation of the value of these durations is derived from the fact that the durations were evenly distributed and not bunched at the 5, 10, 15 and 20 year points as on the death records. The average duration increased in length until 1939

TABLE III
Duration of Diabetes

	N	Average Duration In Years	
1926	87	6.8 ± 0.6	7.6
1927	75	8.5 ± 0.8	
1928	100	7.5 ± 0.6	
1931	87	9.1 ± 0.6	9.5
1932	84	9.9 ± 0.8	
1933	108	9.5 ± 0.6	
1936	187	10.7 ± 0.4	12.0
1937	178	11.4 ± 0.5	
1938	129	12.1 ± 0.5	
1939	597	13.0 ± 0.3	
1940	354	12.8 ± 0.4	
1941	165	11.4 ± 0.5	11.9
1942	165	10.5 ± 0.5	
1943	176	10.9 ± 0.5	
1944	328	14.2 ± 0.4	
1945	209	12.4 ± 0.5	

when a regression occurred, with the lowest point in 1942, followed by a longer duration in the past two years. The averages for the two five-year periods, 1936-1940 and 1941-1945, are practically identical. It is problematical whether the decrease in duration occurred because of war conditions, and a real increase is occurring now, or whether a maximum duration has been attained and chance fluctuations alone have been operating.

MORBIDITY FROM DIABETES

A knowledge of the prevalence of diabetes is of importance in control programs. The reporting of this disease is not compulsory and estimates of morbidity must be substituted. An ideal estimate might be obtained by analyzing the blood sugar of all individuals in sample communities. At the present time such a study is being carried on in Oxford, Massachusetts, by Dr. Wilkerson of the United States Public Health Service. A carefully conducted survey also furnishes a good estimate of diabetes morbidity, although such surveys are believed to give a slight understatement.

A method utilizing mortality statistics is believed to furnish a reasonably accurate estimate of the number of cases of diabetes alive at any one time. An example of this method follows:

If all deaths occurred at the middle point of each year, and if all cases had their onset as many years before death as the average duration of the disease, all the 1942 deaths, for example, would have an onset on July 1, 1930, since 12 years was the average duration. To obtain an estimate of the number of diabetes cases alive on July 1, 1930, sum all the deaths from diabetes for 1931-1941, inclusive, and one-half the deaths for 1930 and 1942, and then multiply this result by the correction factor, 1.562*. Obviously this method can be used only to estimate morbidity in previous years.

* This correction factor was obtained by dividing 100 by 64, the 100 representing the total number of individuals in this study, and the 64 the percentage of cases with diabetes classified as the primary cause on the death certificates.

If no appreciable trend is operating in durations or in the number of deaths, it is possible to obtain a good estimate by multiplying the number of deaths from a trend line at a given year by the period of duration and then by 1.562. With the Massachusetts data it is possible to get good results for recent years by this latter method, and from the summation procedure for the earlier years. The principal difficulty is the choice of the duration to be used.

TABLE IV
Estimated Morbidity of Diabetes in Massachusetts
Rates per 1000

Joslin's Duration	Joslin's Durations Reduced by 25%			
	Deaths with Diabetes x Duration (1)	Summation of the Deaths with Diabetes (2)	Summation from Death Record Duration (3)	Rates from Surveys (4)
			Deaths with Diabetes x Duration (5)	Summation of the Deaths with Diabetes (6)
1927		5.4		3.8
1930		6.0	2.9	4.1*
1932		6.4		4.6
1935		6.6	3.4	4.6**
1938	6.6			4.3 (5.1)***
1940	6.6			4.9
1943	6.7			5.0
1945	6.6			5.6

*Massachusetts Chronic Disease Survey.
**National Health Survey, from unpublished data for Greenfield, Mass.
***Extrapolation of trend of number of deaths to include 1946 and 1947 used in computing this rate.

In Table IV morbidity rates computed from Joslin's durations, from the death record durations, and from Joslin's durations reduced by 25 per cent are shown. Morbidity rates obtained from data collected in two surveys conducted in Massachusetts in 1929-1931 and 1935-1936 are shown in Column 4 of this table (5, 6). Obviously the rates computed from

the death records are too low. While it is believed that rates obtained from surveys may be somewhat low, it is thought they are not as much below the true figure as would be the case if Joslin's durations were used in the computations. While it is impossible to be positive on this subject, the rates computed from the 25 per cent reduction in Joslin's durations are slightly larger than the survey figures and appear to be the most satisfactory. The morbidity rate of 5.0 per 1000 is believed to represent the present situation in Massachusetts.

Unfortunately, the Massachusetts rates cannot be applied to the United States population to determine, with any degree of accuracy, the incidence of diabetes throughout the country, due to differences in age composition, possible differences in duration and in the percentage of primary cases, and probable understatement of the true diabetic death rate in several states. The methods, however, could be used in individual states.

Spiegelman and Marks, in a report on the prevalence of diabetes in the United States, estimated there were at least 500,000 diabetics in 1940 (7). This would correspond to a rate of 3.8 per 1,000, considerably less than the Massachusetts estimate for the same year.

CONCLUSIONS

A perusal of the trend of the diabetic death rates indicates that following the introduction of insulin there was a short drop in the deaths from the disease, but the upward trend was resumed within two years and over a dozen years elapsed before any pronounced change occurred in the trend. For the past eight years the adjusted diabetic death rate has shown no increase and there is even some indication of a regression. The cause of this change is unknown although chronologically it follows the use of protamine zinc insulin. Morbidity, on the other hand, has been on the increase and as yet has not shown a tendency to change. A stationary adjusted death rate and an increasing morbidity rate cannot continue indefinitely. A change must occur in one or the other of these rates.

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Acknowledgement is made to Professor Edwin B. Wilson for reading this paper and offering suggestions in regard to it; but this statement should not be taken as transferring to him any responsibility for the correctness of the material or the results.

Hyperinsulinism with Hypoglycemia Relieved by Removal of Pancreatic Tumor *

by
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HYPERINSULINISM, a relatively rare clinical entity, is to be differentiated from spontaneous hypoglycemia. The two terms are not synonymous. Hypoglycemia is merely a symptom or indication of a disorder involving the carbohydrate metabolism. Spontaneous hypoglycemia may be occasioned by diseases of the liver, endocrines and pancreas as well as by nervous disorders, faulty diet and abnormal living habits. On the other hand, hyperinsulinism is strictly pancreatic in origin. The hypoglycemia results from excessive insulin production through stimulation of the islet tissues or by tumor formation. Harris (1) in an excellent review of the subject includes a simple and totally adequate etiological outline:

1. Functional: overproduction of insulin without evidence of structural change except occasional mild hypertrophy or hyperplasia.

2. Organic: cases with benign or malignant tumors involving the Islands of Langerhans or with inflammatory changes in the pancreas.

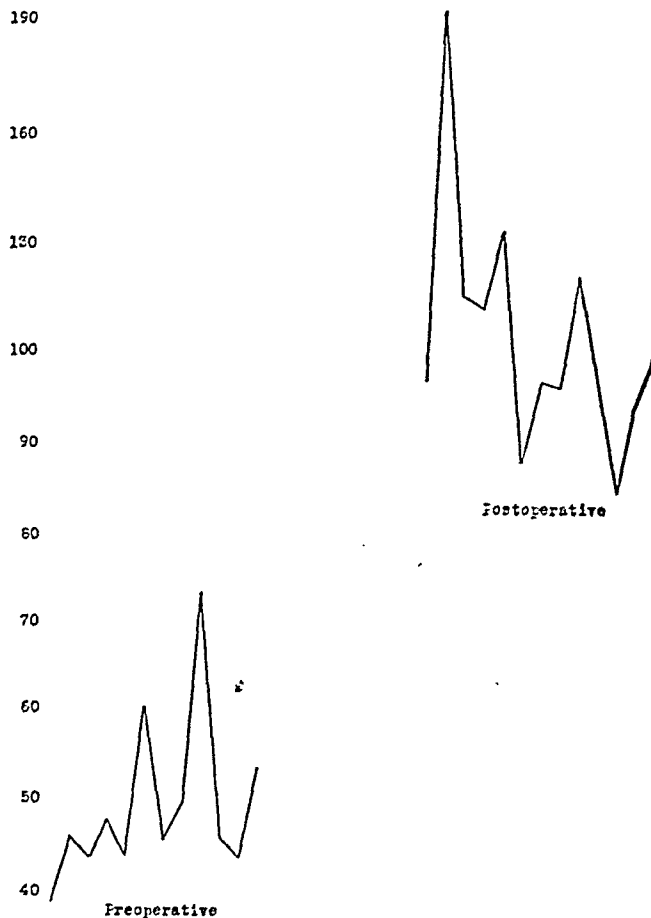
3. Secondary: hypoglycemia due to a disturbance of function of other endocrine glands, especially the pituitary, thyroid and adrenals.

In 1924, Harris (2) observed an otherwise normal patient whose reactions were similar to those of a diabetic receiving excessive amounts of insulin. He proposed a new disease entity which he termed "hyperinsulinism." Although there has been considerable work done on the subject, there have been surprisingly few cases reported. Duncan (3) states that in 18,000 admissions to a Veterans Facility hospital there was an incidence of one case, while the Mayo Clinic, over a period of twelve years, averaged one case per year. The Henry Ford Hospital has experienced three cases in over 500,000 admissions. Those cases in which a pancreatic tumor is the etiological factor are still more rare. Breslin (4) has reported 134 cases in the literature up to 1942. The report herein represents the first case seen at this hospital.

The symptomatology of hyperinsulinism and its diagnostic criteria are well known. The classical Whipple (5) "triad" is still a valuable clinical "yard-stick"—(a) attacks of insulin shock during fasting or while in a fatigue state, (b) blood sugar readings of 50 mg.% or less, and (c) relatively prompt relief following administration of glucose by mouth or parenterally. The past history is of value

since untreated cases tend to have increasingly severe attacks. As pointed out by Harris (1), those patients having mild attacks offer the greatest diagnostic problem. In the so-called "neurotics" with unexplained syncope or convulsive seizures, hyperinsulinism is to be suspected. Numerous tests are in vogue for diagnostic purposes; the glucose tolerance test is always employed and is of great value when properly conducted but is not diagnostic in itself. Conn (6) believes that to be dependable, it must be done under standard conditions. Womack (7) states that a "flat" curve is highly significant if with low peak levels at the one and two hour stages. The preoperative tolerance curve in the case reported is interesting in that at both the one and two hour stages, the blood level was below 45 mg.% (Chart B).

Chart A — Fasting Daily Blood Sugar



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We believe, as is often stated in the literature, the most important diagnostic sign at this time is a persistent fasting sugar level under 50 mg.%. The perfecting of a suitable test for the determination of insulin values in blood as discussed by Dr. C. H. Best (Beaumont Lecture, Detroit, February, 1947) will make a direct laboratory diagnosis possible.

The indications for surgery in hyperinsulinism are: (1) the persistence of symptoms on an adequate medical regimen and (2) the presence of diagnostic criteria, i. e., low blood sugar values and the relief of symptoms by the administration of glucose. At operation a thorough search of the pancreas should be made as the tumors are occasionally multiple; the leaving of one, however small, may continue to produce symptoms. The literature abounds with warnings that in the absence of a tumor, two-thirds to three-fourths of the pancreas should be removed if clinical improvement is to be obtained. Failures may occur even then as in a case reported by David and Campbell (8) in which there was no clinical response after removal of all but three to five grams of pancreatic tissue. Nice surgical judgment is required at the operating table. Holmes, Sworn and Edwards (9) have reported that the literature up to 1946 contains 63 cases treated surgically with complete relief of hypoglycemic symptoms.

CASE REPORT

G. Y., white female, age 40, married, was admitted to the hospital on November 13, 1946 with the complaints of marked craving for sugar, attacks of weakness, flushing of the face, profuse sweating, blurred vision, slurred speech and if not aborted by the ingestion of carbohydrate, syncope lasting from one-half hour to two hours. The attacks occurred at irregular intervals, most often just prior to lunch or dinner or in the early morning hours. These symptoms began in 1942 but during the past year were becoming progressively severe. The past history was interesting in that at the age of 18 the patient was thought to have a mild diabetes with occasional glycosuria. Response to a modified diet was satisfactory.

The family history was non-contributory except for a rather marked tendency to obesity and the presence of diabetes in the paternal grandmother.

Physical examination revealed a well-developed, white female, 5 feet, 8 inches in height with severe obesity, weighing 230 pounds. The head was normal and the neck presented small multiple adenomata in the thyroid. The chest was resonant with normal breath sounds. The heart was normal; no murmurs were heard. Blood pressure 142/84. The abdomen was rounded with a markedly thickened anterior wall — no masses or tenderness elicited. Extremities and pelvis normal.

ROUTINE LABORATORY DATA

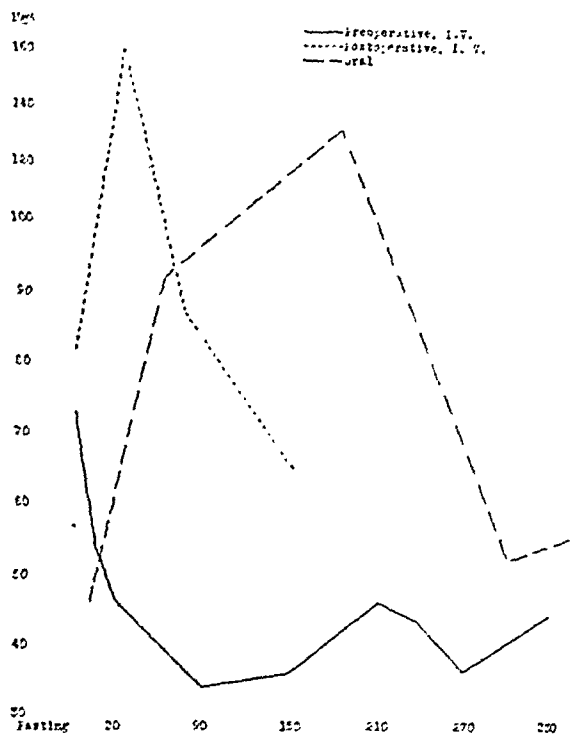
The Kline exclusion test for syphilis was negative. The blood count approached normal — hemoglobin 12.8 grams; RBC 4,180,000; WBC 6,500 with 50% PMN. Urinalysis was negative.

SPECIAL STUDIES

BMR —18% with R.Q. of .71; —13% with R.Q. of .74.
Bromsulphalein 45' and 60' 3%.
Oral hippuric acid 2.76 gm.
Cephalin and cholesterol, negative.
Thymol turbidity, 1 unit.
Thymol flocculation, negative.
Blood calcium, 9.5 mg.%.
Blood phosphorus, 3.42 mg.%.
A series of fasting blood sugar determinations ranged

from 39 to 74 mg.% with an average of 47.7 mg.% (Chart A). Oral and intravenous glucose tolerance curves were completed with difficulty due to hypoglycemic reactions. The intravenous tolerance curve showed a fasting level of 34 mg.% at one and one-half hours and 44 mg.% at 5 hours (Chart B).

CHART B GLUCOSE TOLERANCE



Respiratory quotient determinations ranged from .91 to .72 (Chart C).

Electrocardiogram was normal.

Electroencephalogram subsequent to a glucose tolerance test showed mild abnormalities of alpha rhythm with some indication of paroxysmal irregularity.

X-ray of the skull and sella was negative.

Gastro-intestinal films revealed a normal stomach and duodenal cap.

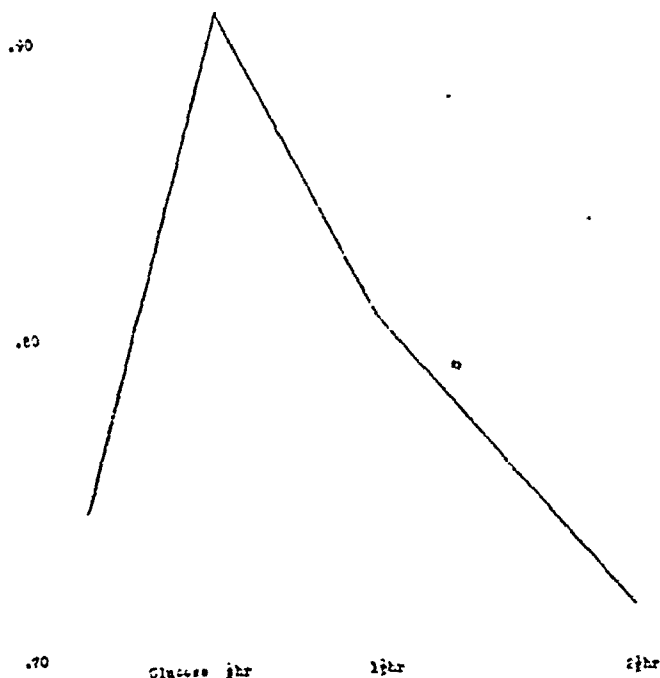
From the time of admission to the day of operation the patient was given a high protein, high fat, low carbohydrate diet with sweetened orange juice available at all times for control of hypoglycemic attacks. The patient was prepared for surgery by administering 300 cc. of 20% glucose intravenously. The operation was performed 11-29-46 by Drs. Roy D. McClure and Brock Brush.

OPERATIVE REPORT

"... The pancreas is explored throughout. The tail and body are normal. In the head just above the beginning of the portal vein we can feel a small circular nodule. . . it is about the size of a table tennis ball and is about 2 cm. in diameter. It is nodular; very easily palpated. Mobilizing it near the pancreas and elevating it, Dr. McClure shelled this nodule out. It seems very vascular, looks different from the rest of the pancreas and comes out in several pieces. . . after carefully palpating the pancreas again and other areas for abnormal pancreatic tissue, we are convinced this is the site of the adenoma and that it has been completely and satisfactorily removed and that there is no other adenoma in the pancreas or any ectopic pancreatic tissue."

That the tumor removed constituted the only pathology present, is substantiated by the complete disappearance of

CHART C RESPIRATORY QUOTIENT



the patient's symptomatology. Through some unfortunate mishap the tissue was not examined by the Pathology Department. On the first postoperative day the fasting blood sugar was 194 mg.% but rapidly subsided to normal (Chart B). The blood diastase on the same day was 37 and declined to 11.9 four days later. The post-operative course was uneventful and the patient was discharged on December 14th on a 1200 calorie, high protein, reducing diet. She was seen in the out-patient department on December 18th at which time the fasting blood sugar was 94 mg.%. By January 31, 1947, she had lost 30 pounds, her blood sugar was 99 mg.% and there had been no symptoms suggestive of hypoglycemia.

DISCUSSION

This patient's obesity is of interest in its development during the time her hypoglycemic symptomatology was present. The patient provided her own insulin for "insulin fattening." The reverse was true even after removal of the tumor — weight loss being accomplished by dietary measures without discomfort. The rather complete liver studies were made to rule out liver deficiency as the cause of hypoglycemia.

SUMMARY

A case of severe hyperinsulinism relieved by removal of pancreatic tumor is reported. The excellent results obtained following the operation is the best proof we have that a solitary tumor existed. The histologic nature of the mass and its malignant possibilities are unknown.

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Moderate Fats in Infectious Hepatitis: A New Concept Based on Recent Advances

By

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FOR CENTURIES efforts have been made to obviate empiricism in the dietary management of diseases and substitute scientific information based on a knowledge of the foodstuffs and the pathologic physiology of the disease process. The ever changing

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diet regimens employed in the treatment of infectious hepatitis is an outstanding example. As recently as 1942, standard texts on dietetics (1-3) have recommended a high carbohydrate, but low protein and fat-free diet.

There is very little evidence that moderate fats are prejudicial to patients with liver disease and the

use of low fat diets appears highly questionable. It is the purpose of this paper to present the advantages of a moderate increase of the fat intake up to 200 grams, in addition to a high carbohydrate and protein intake. This is based on recent advances in pathologic anatomy and physiology and personal observations.

The value of the three main foodstuffs in the treatment of this disease is based on the following established facts:

A. CARBOHYDRATES

The value of carbohydrates in protecting the liver has been adequately established since 1915 (4). As pointed out by Miller and Whipple (5) in studies on protein factors in liver protection, its efficiency is due primarily to sparing protein stores.

B. PROTEINS

The protective action of protein diets in hepatitis has been demonstrated by Goldschmidt, Vars and Ravdin (6) in their work on mice. In 1940, Miller, Ross and Whipple (7) demonstrated that the amino acid methionine, and to a lesser extent cystine, gave adequate protection against liver damage if given before chloroform anesthesia. Later, it was shown that methionine protected protein depleted animals when given up to four hours after chloroform anesthesia, indicating that some viable liver tissue must be present if methionine was to afford protection. There is much evidence to support the belief that the value of the amino acids depends primarily on the sulfur content. The uselessness of choline without cystine has been pointed out by several investigators. Gyorgy (8) suggested that choline and cystine are needed for the synthesis of another substance that may be methionine, which may exert a lipotropic action. Recently urinary methionine excretion has been found increased in cases of liver dysfunction and this has been a guide in prescribing the dosage of this essential amino acid (9). Others have not found this to be of much clinical value.

Microscopic studies by Wachstein (10) showed that marked fatty infiltration occurred in most of the livers of rats on a choline free, protein (methionine)-deficient diet. In liver cells containing much fat, reduction of cytoplasmatic phosphatase activity was seen.

C. FATS

It has long been the custom to prepare the diet devoid as far as practicable of fats. It is the common belief that fats are the least digestible of foods and the most apt to cause symptoms in patients with disease of the liver or gall bladder.

A similar argument in favor of a low protein intake prevailed until recently (1941) since it was believed that the impaired liver could not properly metabolize the split protein products (1-3, 11). At the present time it is recommended in military installations not to restrict dietary fats too extensively but to provide for an intake of 70 to 90 grams (12). From our observations, it is felt that patients can

tolerate an even larger intake of fat.

It is the purpose of this paper to point out the disadvantages of fat-free and low fat diets and the advantages of a further increase in the amount of fats up to 200 grams. A discussion of the requirements and functions of dietary fats and pathologic anatomy and physiology is included in view of recent important advances affecting the treatment of infectious hepatitis.

FUNCTIONS OF DIETARY FATS

An understanding of the normal function of dietary fats is essential to the physiologic approach of infectious hepatitis dietotherapy.

These mainly cover the glycerides which are hydrolyzed to glycerol and fatty acids with resynthesis on absorption (2). The former substance is metabolized as though it were a carbohydrate, the latter under β -oxidation is converted to carbon dioxide and water. Neutral fat is stored in various depots for reserve energy. Waxes are not affected by lipolytic enzymes and are of no apparent value to the body. The destruction and synthesis of cholesterol (animal sterol) and phospholipids are not well understood but they are not primarily a source of energy. They enter into the structural framework of protoplasm constituting tissue fat as opposed to storage fat. Plant sterols or phytosterols are probably not absorbed at all from the intestinal tract (13). Patients can synthesize saturated fatty acids from sources other than dietary fat but are unable to synthesize unsaturated fatty acids to a sufficient extent to maintain the normal degree of unsaturation of the blood lipids (14).

The various animal fats ("rancid fats") and vegetable oils differ strikingly from one another in their physical characteristics and chemical behavior (Table 1). This is of the utmost importance in selecting the

TABLE 1: RELATIVE PHYSICAL DIFFERENCES OF FATS AND OILS

FAT	M.P. (in C)	Iodine No.	Saponification Value
Butter Fat	28-33	26-38	220-233
Pork Fat	36-46	50-70	195-197
Beef Fat	40-48	36-48	192-200
Olive Oil	2-10	78-91	185-194
Human Fat	17.5	57-66	193-199

proper fats in the diet. These differences are mainly determined by the relative proportions of the glycerides of palmitic, stearic and oleic acids contained in each fat. The glycerides of oleic acid have the lowest melting point while those of stearic acid have the highest. Therefore, olive oil, which consists largely of glycerol trioleate, is fluid at ordinary temperatures, while mutton fat, which has a high content of glycerol tristearate, is practically solid. Even a small admixture of triolein reduces the melting point of a fat to a very considerable degree. However, the unsaturated vegetable oils, such as olive oil, fail to furnish the nutritive equivalent of butter and animal fats. The latter group furnishes accessory foodstuffs which are essential for growth and health maintenance, while the vegetable oils are lacking in these. When fuel value alone is considered they are equivalent.

lent. Besides only a small proportion of the total fat consumption is necessary to furnish these accessory foodstuffs and they can be supplied by the butter fats. Milk fat consists in large part of olein and palmitin, and to a lesser degree of stearin, butyrin and caproin. Butter fats have the highest saponification value and one of the lowest melting points. It is for these reasons that oils and dairy fats are stressed in the moderate fat diet.

NORMAL FAT REQUIREMENTS

Since adequate experimental data are not available, it is difficult to fix a safe lower limit for fat ingestion normally. The average 3000 calorie diet contains about 100 grams of fat, approximately 30 per cent of the total calories. Diets with a fat content as low as twenty grams per day are often termed fat free or low fat diets since it is extremely difficult to prepare a diet that is totally devoid of fats.

PATHOLOGIC PHYSIOLOGY OF LIVER DAMAGE

The experimental studies of Mann (16) have been of the greatest importance in evaluating the hepatic functions. It was found that the following physiologic processes ceased immediately on total removal of the liver: maintenance of normal level of blood sugar, formation of urea, oxidation of uric acid to allantoin, de-aminization of amino acids, formation of prothrombin, fibrinogen and plasma albumin, bile secretion for fat digestion, antiseptic action and inhibition of intestinal bacteria, and detoxifying function in removing poisons from the blood stream. A physiologic process that was considered modified was the ability to store sugars. The chief physiologic functions of bile have been summarized by Ivy and Berman (17).

PATHOLOGIC ANATOMY

The diets in infectious hepatitis are based on a pathologic picture that has long been misunderstood, primarily because of the paucity of postmortem material. Hence it has been the common belief that fatty changes of the liver and impaired bile physiology preclude the use of fats.

It was not until World War I that Eppinger (18) showed that the livers in hepatitis were involved without obstruction by duodeno-biliary catarrh. Other studies mentioned in standard books on pathology showed that fatty changes were not a part of the disease process. The confusing finding of positive fat stains has been explained by Endicott (19) who demonstrated that the stain is picked up by two "waste-pigments," lipofuscin and ceroid. Biopsy studies in various stages of the disease showed a picture characterized by acute necrosis and autolysis beginning at the centre of the lobules, disorganization of the liver cell columns, and leukocytic and especially histiocytic infiltrations into the portal zones. Damage and disorganization may become so widespread that one may wonder how recovery can take place. Biopsies on patients erroneously operated upon showed

cloudy swelling with green staining by bile pigments. Exhaustive studies by Lucke (22) on 125 fatal cases of infectious hepatitis have shown no evidence of fatty changes such as are characteristically seen in yellow atrophies due to chemical poisons, bacterial toxins, yellow fever or eclampsia. The rapidity and completeness of cell destruction with little or no involvement of the reticular framework is a distinguishing feature of epidemic hepatitis.

The disease process differs from that caused by hepatotoxic chemicals which are frequently associated with fatty changes (23). Hence, the significance of toxic agents producing fatty changes (5-8), such as chloroform, does not hold for infectious hepatitis. Recent studies of livers in homologous serum jaundice have shown similar pictures with necrosis, atrophy and varying degrees of regeneration.

ADVANTAGES OF MODERATE FATS IN THE DIET

The arguments in support of a moderate fat diet are not meant to preclude the importance of continuing a diet high in carbohydrates and proteins. This has been adequately established by numerous investigators. Wilson et al. (24), in a recent dietary study of 103 treated cases and controls of infectious hepatitis could find no evidence that a high-fat diet (202 grams fat) had an intolerant or harmful effect on the course of the disease. Serum bilirubin, hippuric acid synthesis and the clinical course were used in comparison studies. Until adequate experimental evidence can be adduced showing that diets which contain a moderate amount of fat are injurious to patients with acute non-obstructive disease of the liver, it seems unwise to prescribe diets which provide as little as 25 grams of fat daily (25). Of course, if there is previous fat intolerance, overweight or associated gall bladder disease, a low fat diet may be indicated. Based on recent advances in the knowledge of infectious hepatitis and our clinical observations, the following advantages of an increased fat intake (up to 200 grams) are stated:

1. HIGH CALORIC VALUE

Because of the chronicity of illness and the post-infectious asthenia, weight loss was considerable in the majority of the patients. Increased fats afforded a higher caloric intake in more concentrated form with less bulk and moisture content. They have a great satiety value and Starling (26) claims the digestive system of Western peoples has adjusted itself to fats constituting about one-fourth the caloric intake. By contributing a large amount of energy, it relieves the intestinal tract of the necessity for dealing with an excessive amount of carbohydrate and to a lesser extent spares protein.

2. IMPORTANCE OF FATTY ACIDS

Brown and his associates (28) have shown that even the normal human subject is unable to fabricate the highly unsaturated fatty acids and, therefore, they must be provided in the diet. When preformed fatty acids are available from dietary fat they ap-

pear to be used for body fat synthesis almost to the exclusion of acids which might otherwise be made from carbohydrate and protein (27). It was shown by Burr and Burr (29) that independent of vitamin supply, a fat-free diet in rats regularly resulted in renal lesions and other evidences of disease. Evans and Lepovsky (30) found that successful gestation and lactation in these animals were impossible and that male sterility occurred when the diet was entirely fat-free. These could be avoided by the addition of certain essential fatty acids. The hypothesis is advanced that warm-blooded animals in general cannot synthesize appreciable quantities of unsaturated fatty acids. It is also believed that the high carbohydrate, high protein diet are ordinarily contributing factors to poor health because of their paucity of these fatty acids (29). In his excellent review, Rapport (31) states that excess ingestion of carbohydrates and even protein is converted into fat. Hence, the body is called upon for extra anabolic processes during the acute phase of the disease process.

3. DIGESTIBILITY OF FATS

A possible objection to ingestion of fats of exogenous origin would be the low output of bile acid in hepatic disease. Since the liver produces no digestive fat ferments of its own but supplies the bile salts for lowering of surface tension for emulsion

individual bile constituents. Cholic acid is the active principle in bile acids with a choleric action. Generally, ten grains (0.6 gm.) of bile salts may be administered with each meal. Desoxycholic acid in one grain (0.065 gm.) doses is occasionally employed to increase lipase activity, decrease surface tension and increase fat absorption. Ketocholic acids in three grain doses (200 mg.) increase the volume and flow of thin bile, flushing the passages with their natural solvent. Fats in themselves have a cholagogue effect. In addition, the presence of fats in the stomach allows for slower evacuation and more complete gastric digestion of food, especially the proteins. Cholagogues and choleretics were not employed routinely in our patients because improved elaboration of fat in the liver by this means is still uncertain and the patients generally showed a remarkable tolerance for selected fats.

4. INCLUSION OF FAT SOLUBLE VITAMINS

The use of adequate fats minimizes the need for supplementary vitamin therapy since the fat soluble vitamins are not excluded from the diet. On the fat-free diet, vitamin losses during the prolonged course of the disease may result in subclinical manifestations of vitamin deficiencies. Supplementation of fat soluble vitamins A, D, E and K then may be

WEEKLY TRAY CHECK CHART (35)

Calories Served	4250			4375			4120			4242			4006			4621			4532			Daily Caloric Average
NAME	B	D	S	B	D	S	B	D	S	B	D	S	B	D	S	B	D	S	B	D	S	
F. R.	1	1	1	1	1	1	1	X	1	1	1	1	1	1	1	X	1	1	X	1	1	4330
J. D.	X	1	1	X	1	1	X	X	1	X	1	1	X	1	1	X	1	1	X	1	1	4372
B. L. C.	2-3	1	1	2-3	1	1	1	X	1	1	1	X	2-3	1	1	2-3	1	1	1	1	X	4117
D. O. R.	X	1	1	X	1	1	1	1	1	1	X	X	X	1	X	1	1	1	1	1	X	4422
S. M.	1	2-3	1	1	1	1	X	1	1	1	1	1	1	2-3	1	2-3	1	1	1	1	X	4103
E. M. L.	X	1	X	X	1	1	1	1	2-3	1	1	1	X	1	2-3	1	1	1	1	1	1	4317
J. R.	X	1	1	X	1	1	X	1	1	X	1	X	X	1	1	X	1	1	X	1	1	4415
F. S. O.	1	1	1	1	1	1	1	X	1	1	X	1	2-3	1	1	1	1	1	1	1	1	4327
L. B.	2-3	1	2-3	1	2-3	1-2	X	1	1	1	2-3	1	1	1	2-3	1	1	1	2-3	2-3		4003

LEGEND:

B D S — Breakfast, Dinner, Supper

1 — Entire Meal Ingested

1-2 — Half Meal Ingested

2-3 — Two-thirds Meal Ingested

X — Entire Meal plus Second Helping

NOTE: Supper includes 8 P. M. feeding of Sandwich, fruit juice and milk.

and greater exposure to the pancreatic lipase, this impaired function of the liver can be replaced by oral bile salts or the cholic acid group when necessary. Actually, pancreatic lipase is active in the absence of bile acids but it is increased threefold in the presence of bile (17). Diarrhea due to increased fats was not encountered. Presumably it is due to varying degrees of enteritis caused by poorly emulsified fats and irritating fatty acids. Steatorrhea did not occur in any of the cases. Actually even a limited amount of bile salts can facilitate the absorption of an almost unlimited amount of fat (6). Of the cholagogues and choleretics, the former increase the volume of bile flow by contracting the gall bladder musculature and the latter increases the quantity of

come necessary in the fat-free diet. Common symptoms of vitamin A deficiency include malnutrition, impaired vision, susceptibility to infections and nervous disorders and metaplasia of the mucous membranes with keratinization. The effects of vitamin D deficiency are too well known to describe here. Vitamin B may be supplemented in doses of 10 mg. daily. Larger quantities are unnecessary and, in fact, have been thought harmful. Yeast tablets produced a sense of fullness in many patients. There is a sparing action of food fats on the vitamin B complex (27). The optimal normal requirements of many vitamins are still unsettled and therefore makes it difficult to indicate exact dosages and uses for all of them even in normal health.

5. THE MORALE FACTOR

Patients with a long standing objection to eating are likely to do badly. During the initial period of extreme nausea, patients were given as much homogenized milk as they desired. This type of fat was well tolerated in the acute phase and hunger seemed to be satisfied. The finer size and distribution of fat aided its digestibility. Small amounts of fresh butter and other dairy fats were then added to the diet. The total fat was finally brought up to 200 grams since tolerance for more calories increased after the acute phases subsided. The butter fats and oils were the main fat sources. All visible animal fat was trimmed from meats and preference was given to beef. In carefully checking plate waste (32), all foods were consistently found consumed to a greater degree than previously unless there was a personal dislike for a particular food item. A surprising number of second helpings were requested and completely consumed by many of the patients. Increased fats made the foods more palatable. Fats and fat-bearing food stuffs have always held an important place in the human diet. The monotony of diet restriction was relieved by approaching the usual type of meal to which they were accustomed. Special emphasis was given to colorful and attractive trays. An important advantage was that these were much more easily prepared in the diet kitchen than the low fat and fat-free diets. A reasonably wide choice of foods was possible without fat restrictions. Homogenized milk was preferred to banana milk because of the tiring distinctive flavor of the latter. Morale was distinctly improved, with decreased psycho-neurotic tendencies usually associated with the post-infectious asthenic state and prolonged bed rest. The avoidance of irritating food, condiments and alcohol is important. Gas-forming vegetables such as beans, cabbage, turnip, rutabaga and broccoli, etc., are best omitted.

6. CALCIUM AND IRON METABOLISM

Over long periods on fat-free diets, calcium deficiencies may result in withdrawal of lime from the bones. This is associated with low vitamin D intake. The elimination of a large proportion of dietary calcium in the form of calcium soaps in the feces may occur from inadequate digestion of fats and defective assimilation of the higher fatty acids (palmitic and stearic). This does not occur when moderate fats are included with or without bile salt therapy. Bile acids also aid in the absorption of iron.

ADJUNCTS IN TREATMENT

1. BED REST: Early and adequate bed rest decreases the severity of the disease and shortens the clinical and convalescent periods (33, 34). This is probably the most important single factor in the proper management of the disease. Too early resumption of activity may result in recurrences and increasing hepatomegaly. The criteria for recovery are a period of bed rest for at least three weeks, normal liver size or slight increase without tenderness or symptoms, absent direct immediate Van den Bergh reaction and serum bilirubin under 2 mg. per cent.

2. NAUSEA AND VOMITING: If nausea and vomiting are severe, 5 to 10 per cent intravenous glucose solution may be necessary. Plasma, whole blood or protein hydrolysates may be required to bolster protein intake in severe attacks. Barker (34) advised two units of plasma daily. The blood protein levels are the guide.

3. VITAMIN SUPPLEMENTS: Hemorrhagic phenomena associated with reduced plasma prothrombin levels required parenteral vitamin K in 2 mg. doses. Ten mg. of thiamine chloride orally each day is adequate. Larger doses are thought to be harmful. Other vitamins may be added but their excess use is also thought to be deleterious.

4. METHIONINE AND CHOLINE: The present consensus of opinion is that these amino acids actually have very little measurable effect on the clinical course of the disease. When employed, choline has been used in doses of three grams daily; methionine up to ten grams daily.

5. CHOLAGOGUES AND CHOLERETICS: These have been considered under the digestibility of fats.

6. IMMUNE SERUM GLOBULIN (Human): It has been demonstrated that the gamma globulin fraction of pooled human serum collected from adults contains some protective substance, probably an antibody. If given during the incubation period this material may occasionally be effective in preventing or ameliorating the disease. Its therapeutic effects have been disappointing in management of cases of "homologous serum jaundice." There are conflicting reports as to its effectiveness even as a prophylactic agent, except in epidemic infectious hepatitis. Two illustrative cases follow:

CASE 1. PRESENT ILLNESS: One week before admission the patient complained of general malaise, headache and backache. There were no gastro-intestinal symptoms other than mild anorexia. The urine became darker but the stools remained normal in appearance. Past history revealed no gall bladder disease, malaria, blood dyscrasia, chills, blood or plasma transfusions or jaundice. Family history was non-contributory.

PHYSICAL EXAMINATION: revealed a 37 year old, well developed, well nourished white male with slight icterus of the skin and sclera. Heart and lungs were negative. Liver edge was not palpable but there was very slight tenderness on direct percussion. The spleen was not enlarged. The remainder of the examination was negative.

LABORATORY STUDIES: Urine examination was negative except for positive bile and positive methylene blue test. Stool examination revealed no ova or parasites and there was a positive test for bile and one plus occult blood with a trace of mucus. No pathogenic organisms were found on repeated stool cultures. On admission, the white cell count was 8,350 cells with 58 per cent neutrophils, 40 per cent lymphocytes and 2 per cent eosinophiles. Hemoglobin was 88 per cent. Heterophile antibody test revealed no titre. Sedimentation rate was 21 mm. in one hour. Icterus index was 17. Electrocardiogram was negative except for sinus tachycardia with a rate of 107 per minute and a PR interval of 0.16 seconds.

TABLE 2: FAT FREE MENU

FOOD	Weight Grams	Calories	Protein Grams	Fat Grams	CHO Grams	Calcium Mgs.	Phosphorus Mgs.	Iron Mgs.	Vitamin A I. U.	Thiamin Mgs.	Riboflavin Mgs.	Niacin Mgs.	Ascorbic Acid, Mgs.	Vitamin D I. U.
BREAKFAST														
Grapefruit Juice	200	94	0.8	0.4	22	42	40	0.6	20	.04	.04	0.36	68	
Canned Pear Halves (2)	100	75	0.2	0.1	18	8	18	0.2	30	.01	.02	0.13	2	
Cornflakes	20	72	1.6	0.1	16	5	11	0.3		.08	.02	0.39		
Dry Toast (1 thick)	40	104	3.4	0.8	21	20	64	1.1		.11	.10	0.12		14
Jelly (1 T.)	20	52			13	3	2	0.1	2			0.03		
Skim Milk	250	93	9.3	0.5	13	305	240	0.6	50	.05	.45	0.28	3	
Coffee with sugar	12	48			12									
10 A. M.														
Pineapple Juice	200	110	0.4	0.4	26	16	20	0.2	100	.10	.04	0.36	18	
Hard Candy	50	198			49									
DINNER														
FF Broiled Steak	100	174	30.0	6.0		17	323	4.5	40	.11	.21	4.52	1	
FF Spaghetti w tomatoes	170	121	4.0	1.9	21	8	41	0.6	470	.03	.02	0.34	9	
FF Spinach	100	30	2.3	0.5	4		36	2.0	5200	.02	.08	0.31	11	
H.B. Egg Halves (2)	50	70	5.7	5.1		24	99	1.2	440	.06	.17	0.03		25
FF Green Lima Beans	100	55	3.3	0.2	10	14	79	1.2	380	.12	.06	0.90	9	
Bread (1 thick)	40	104	3.4	0.8	21	20	64	1.1		.11	.10	0.12		14
Jelly (1 T.)	20	52			13	3	2	0.1	2			0.03		
Fresh Orange Sections	100	49	0.9	0.2	11	24	18	0.4	250	.08	.03	0.22	45	
Assorted Cookies (2)	25	98	1.4	3.7	15	6	14	0.2		.01	.01	0.15		
Tea with sugar	12	48			12									
Skim Milk	250	93	9.3	0.5	13	305	240	0.6	50	.05	.45	0.28	3	
2 P. M.														
Tomato Juice	200	46	2.0	0.4	8	14	30	0.8	1700	.10	.06	1.50	26	
Hard Candy	50	198			49									
SUPPER														
Graham Crackers (2)	25	104	2.0	2.5	19	5	50	0.5		.01	.03	0.40		
FF Split Pea Soup	200	84	5.1	0.3	15	18	99	1.7	55	.14	.05	0.77		
Crackers (4)	20	84	1.9	1.9	15	4	20	0.3		.03	.01	0.12		
FF Beef Roast	100	174	30.0	6.0		17	323	4.5	40	.11	.21	4.52	1	
FF Mashed Potatoes	100	85	2.0	0.1	19	9	49	0.7	40	.11	.04	1.21	12	
FF Beets	100	55	1.5	0.1	12	18	28	0.7	10	.01	.02	0.20	3	
Lettuce Salad w MO dress.	50	10	0.6	0.1	2	11	13	0.3	100	.03	.02	0.09	3	
Bread (1 thick)	40	104	3.4	0.8	21	20	64	1.1		.11	.10	0.12		14
Jelly (1 T.)	20	52			13	3	2	0.1	2			0.03		
Applesauce	100	82	0.2	0.1	20	4	7	0.2	50	.01	.01	0.04	1	
Coffee with sugar	12	48			12									
Skim Milk	250	93	9.3	0.5	13	305	240	0.6	50	.05	.45	0.28	3	
TOTAL	2959	134.0	34.0	528	1248	2236	26.5	9081	1.69	2.8	17.85	218	67	
Recommended Dietary Allowance for Sedentary Man of 70 Kg.	2500	70.0			800	1320	12.0	5000	1.50	2.2	15.00	75	200	

CLINICAL COURSE: The patient improved gradually for 19 days and then suffered a relapse with return of malaise, anorexia and slight temperature rise to 99.2 degrees F. The icterus index finally reached normal limits 13 days after this exacerbation.

TREATMENT: On admission, patient was given a high carbohydrate, high protein and low fat diet with banana milk added four times daily. One multi-vitamin capsule re-enforced with five mgm. of thiamine chloride was given three times daily after meals. One tablet of Synkavite (vitamin K) was given daily. In addition, hard candies were fed between meals. At the time of the exacerbation, patient was given clysis of one liter of 10 per cent glucose solution with 10 mg. thiamine chloride intravenously daily for four days. During the exacerbation, the diet was changed to a high protein, high carbohydrate and moderate fat content. Since the patient was a mess sergeant, his opinions relative to subjective complaints were especially informative. The original diet (Table 2) was so unpalatable that much food was left on the tray at each mealtime. The banana milk formula was soon tiring because of its distinctive flavor, depriving the patient of a high protein intake. A rapid return of appetite and weight increase ensued. Morale was con-

siderably affected by the addition of moderate fats to the diet (Table 3).

CASE II. PRESENT ILLNESS: Four days previously, the patient had a violent attack of abdominal cramps followed by vomiting with inability to retain any food. He then noticed that his urine became much darker but the stools did not change color nor did he develop any diarrhea or constipation. Past history and family history were non-contributory.

PHYSICAL EXAMINATION revealed a 34 year old white officer with definite icteric tinge of the sclera and skin. Heart and lungs were negative. Although the liver and spleen were not palpable there was definite tenderness over the right upper quadrant. There was no rigidity or masses. Remainder of examination was negative.

LABORATORY STUDIES showed a white count of 6,300 with 50 per cent neutrophils, 49 per cent lymphocytes and 1 per cent eosinophiles. Hemoglobin was 104 per cent. Urine was essentially negative except for a positive test for bile. Icterus index was 22 and the direct Van den Bergh test was positive immediate. Kahn test

TABLE 3: HIGH PROTEIN, MODERATE FAT MENU

FOOD	Weight Grams	Calories	Protein Grams	Fat Grams	CHO Grams	Calcium Mgs.	Phosphorus Mgs.	Iron Mgs.	Vitamin A I. U.	Thiamin Mgs.	Riboflavin Mgs.	Niacin Mgs.	Ascorbic Acid, Mgs.	Vitamin D I. U.
BREAKFAST														
Grapefruit Juice	200	94	0.8	0.4	22	42	40	0.6	20	.04	.04	0.36	68	
Canned Pear Halves (2)	100	75	0.2	0.1	18	8	18	0.2	30	.01	.02	0.13	2	
Cornflakes	20	72	1.6	0.1	16	5	11	0.3		.08	.02	0.39		
Toast (1 thick)	40	104	3.4	0.8	21	20	64	1.1		.11	.10	0.12		14
Butter (1 pat)	10	73		8.1		2	2		319			0.01		8
Jelly (1 T.)	20	52			13	3	2	0.1	2			0.03		
Soft Eggs (2)	100	140	11.4	10.2		48	198	2.4	880	.12	.34	0.06		50
Whole Milk (2)	500	346	17.6	19.6	26	590	466	1.0	850	.20	.90	0.56	5	10
Coffee with sugar	12	48			12									
10 A. M.														
Whole Milk (1)	250	173	8.8	9.8	13	295	233	0.5	425	.10	.45	0.28	3	5
Hard Candy	50	198			49									
DINNER														
Broiled Steak with juice	200	348	60.0	12.0		34	646	9.0	80	.22	.42	9.04	2	
Spaghetti with tomatoes	170	121	4.0	1.9	21	8	41	0.6	470	.03	.02	0.34	9	
Buttered Green Limas	100	55	3.3	0.2	10	14	79	1.2	380	.12	.06	0.90	9	
H.B. Egg Halves (2)	50	70	5.7	5.1		24	99	1.2	440	.06	.17	0.03		25
Bread (1 thin)	20	52	1.7	0.4	11	10	32	0.6		.06	.05	0.06		7
Butter (3 pats)	30	219		24.3		6	6		947			0.03		24
Jelly (1 T.)	20	52			13	3	2	0.1	2			0.03		
Fresh Orange Sections	100	49	0.9	0.2	11	24	18	0.4	250	.08	.03	0.22	45	
Assorted Cookies (2)	25	98	1.4	3.7	15	6	14	0.2		.01	.01	0.15		
Whole Milk (2)	500	346	17.6	19.6	26	590	466	1.0	850	.20	.90	0.56	5	10
2 P. M.														
Whole Milk (1)	250	173	8.8	9.8	13	295	233	0.5	425	.10	.45	0.28	3	5
SUPPER														
Split Pea Soup	200	84	5.1	0.3	15	18	99	1.7	55	.14	.05	0.77		
Crackers (4)	20	84	1.9	1.9	15	4	20	0.3		.03	.01	0.12		
Lean Beef Roast	100	174	30.0	6.0		17	323	4.5	40	.11	.21	4.52	1	
Mashed Potatoes	100	85	2.0	0.1	19	9	49	0.7	40	.11	.04	1.21	12	
Head Lettuce Salad with	50	10	0.6	0.1	2	11	13	0.3	100	.03	.03	0.09	3	
French Dressing w veg. oil	20	64		7.0										
Bread (1 thin)	20	52	1.7	0.4	11	10	32	0.6		.06	.05	0.06		7
Jelly (1 T.)	20	52			13	3	2	0.1	2			0.03		
Applesauce	100	82	0.2	0.1	20	4	7	0.2	50	.01	.01	0.04	1	
Graham Crackers (2)	25	104	2.0	2.5	19	5	50	0.5		.01	.03	0.40		
Whole Milk (2)	500	346	17.6	19.6	26	590	466	1.0	850	.20	.90	0.56	5	10
Butter (2)	20	146		16.1		4	4		638			0.02		16
NIGHT FEEDING														
Roast Beef Sandwich														
Lean Beef	100	174	30.0	6.0		17	323	4.5	40	.11	.21	4.52	1	
Bread (2 thin)	40	104	3.4	0.8	21	20	64	1.1		.11	.10	.12		14
Lettuce (1 leaf)	25	5	0.3		1	6	7	0.2	50	.02	.01	.05	2	
Tomato Slices	50	12	0.5	0.2	2	4	11	0.3	565	.03	.02	0.34	13	
Mayonnaisse (w veg. oil)	10	66	0.1	7.3		1	4	0.1	21					
Whole Milk (1)	250	173	8.8	9.8	13	295	233	0.5	425	.10	.45	0.28	3	5
TOTAL		4775	251.0	205.0	487	3045	4377	37.6	9246	2.5	6.1	26.71	192	210
Recommended Dietary Allowance for Sedentary Man of 70 Kg.		2500	70.0			800	1320	12.0	5000	1.5	2.2	15.00	75	200

was negative. Temperature, pulse and respirations were normal throughout.

TREATMENT: Patient was placed on high carbohydrate, high protein, low fat diet with banana milk five times a day. Supplementary vitamins were added, reinforced with 10 mgm. of thiamine chloride daily.

COMMENT: The patient found that he quickly tired of the banana milk feedings and left much food on his tray. He found the diet (Table 2) unpalatable and had great difficulty in consuming an adequate amount of calories. Upon the addition of increased fats to the diet

(Table 3) the patient began to eat all of the food on his tray with rapid regain of his weight and strength.

CONCLUSION

A moderate increase of fats up to 200 grams in the dietary treatment of infectious hepatitis is advocated in light of recent advances in pathologic anatomy and physiology and clinical observations.

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Case Reports from Soper-Joslyn Clinic, St. Louis

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CASE NO. 1

Widow aged 67 came under observation December 11, 1945. Blood pressure 200 over 90. Complained of severe backache and stiffness of both knee joints. X-ray of the lower spine and knees showed the presence of nodules characteristic of the degenerative form of arthritis. Her finger joints were enlarged with typical Heberden nodes.

Blood count was as follows: Hemoglobin, 70 per cent; Erythrocytes, 4,330,000; Leucocytes, 5,800. Wasserman and Kahn negative. Urinalysis revealed nothing abnormal.

She was placed on a diet list which included all vegetables and all fruits. Bread was limited to four slices of whole wheat bread daily. She was permitted to eat the white-of-egg desserts, but everything containing the yolk of eggs, all meats and all internal organs were excluded. In fact, she followed our typical low cholesterol diet. This treatment is based upon the fact that cholesterol deposits in the arteries and the joints were responsible for the high blood pressure and degenerative arthritis.

Although her basal metabolism test was within normal limits, her skin was rough and nails brittle. She was placed upon one grain of thyroid taken in the morning upon arising and given the Squibb's Brewers' Yeast Powder, two teaspoonfuls once daily, for the Vitamin B content.

Her back and knees improved rapidly and by February 26, 1946, her blood pressure was 150 over 70. Administration of thyroid was stopped. At that time her diet was increased to include the lean portion of beef, chicken, turkey, lamb and baked fish once daily, avoiding all gravies.

When she reported December 2, 1946, her blood pressure was 140 over 70 and she was free from all pain. Her weight was 129 pounds.

We see many cases of this combination of hypertension and degenerative arthritis that are completely relieved by this method of treatment. Both thyroid and iodine are cholesterol solvents and one or the other should be administered regardless of the basal rate.

CASE NO. 2

Female aged 64 had been under our care for minor digestive disturbances and bronchitis for the past five years. January 17, 1947, she came to the office with a temperature of 102.5 degrees complaining of pain in the upper part of the right chest. She had no cough, but had lost her appetite and the pain was disturbing her. Complete physical examination of the chest revealed absolutely no lesion whatsoever, no dullness on percussion, no rales heard. This finding was corroborated by two other members of the staff. It really appeared to be a case of intercostal neuralgia. However, because of her rise in temperature we had an x-ray of her chest which revealed a shadow indicating consolidation in the lower part of the upper right lobe.

She was sent home and a practical nurse was engaged who fed her every two hours. She was given a tablet Grain 7.5 sulfathiazole every three hours with a glassful of water. In two days' time the temperature had subsided entirely and she began to cough and expectorate blood and mucus characteristic of lobar pneumonia. A microscopic examination of the smear revealed a pneumonococcus, negative for tubercle bacilli. Her appetite improved. She was kept in bed for one week's time. She had taken 20 of the sulfa tablets which were now discontinued and she was placed on liquid peptonoids and creosote, 2 drams every two hours. She returned to her work as saleswoman.

Reported again to the office on February 25, 1947. Her chest was again x-rayed and a slight thickening of pleura corresponding to the lower surface of the pneumonic process was disclosed. She was free from cough or discomfort and regained her weight and strength.

This is truly a case of a typical lobar pneumonia, which could only be diagnosed by x-ray of the chest.

CASE NO. 3

Diabetes mellitus. Patient male aged 58, 5 foot 7 in height, weight 210 pounds. Had been under treatment elsewhere for diabetes for four years. He was given a diet of large fat content and was taking 40 units of insulin daily. His blood pressure was 210 over 110. He was obese, the liver enlarged, a hand's breadth below the rib margins. His skin was dry and he suffered from itching, headache and vertigo. The basal metabolism rate was minus 10, fasting blood sugar 180, NPN 36.

He was placed on a diet of low cholesterol content, consisting chiefly of fresh vegetables and fruit. Fresh brewers' yeast powder was administered to maintain the Vitamin B complex. Two grains of desiccated thyroid was given in the morning upon arising. Thyroid is a cholesterol solvent. We frequently see subthyroid patients who have been taking large doses after meals. The acid content of the stomach quickly digests the thyroid and no results are produced; a much smaller dosage in the fasting stomach is effective.

The patient lost weight rapidly, his headache and

vertigo disappeared, his skin cleared up and in two months' time his liver was normal in size, his blood pressure was reduced to 140 over 80. The insulin was gradually reduced. In six months' time his fasting blood sugar was 80. The urine was free from sugar and the insulin was discontinued. His diet was increased to one portion of lean meat once daily and a fairly normal carbohydrate content, the egg yolk, internal organs, butter, pork, cream and other fats of high cholesterol content were avoided.

We see many cases of this character who improve when the high fat diet is discontinued, and iodine or thyroid is administered.

The occult blood test in the feces. This test is of extreme value. We have made it a rule that no matter what the patient complains of a routine analysis of the feces should be done in every case. The gastric ulcer patient will soon show a negative test. If it remains positive for several weeks under strict ulcer-cure regimen a diagnosis of malignancy is made and operation advised. Many patients have been saved by this method. We have collected now 78 cases with persistent occult blood in the feces in which x-ray examination of the entire gastro-intestinal tract has been negative, palpation negative, patient sustained no weight loss and no loss in appetite. The diagnosis finally established was malignancy and was confirmed by operative procedure. In 35 of the cases a lesion was located in the stomach, 32 in the colon, 9 in the small intestine and 2 in the oesophagus. All of these were early in character and all successfully removed by surgery without a single fatality.

One remarkable case not included in this list occurred in a female aged 36 who had slight digestive disturbances, no weight loss, but persistent occult blood reaction in the feces. Operation disclosed an inoperable carcinoma in the second portion of the duodenum which finally resulted in metastasis and death.

In all of these cases it is very important to exclude the presence of bleeding from other sources such as nasal sinuses, throat, gums, hemorrhoids, cervix, and rectal and sigmoid polyps. Even in a virgin with a strong hymen we find that we can introduce a three-eighths-inch vaginoscope with the patient in the knee-chest posture and have a good view of the cervix. We find benign polyps in the rectum and sigmoid can be readily destroyed by the diathermy spark.

We employ a modification of the Guaiac test for occult blood, inasmuch as we found that the other tests were really too delicate in character. The test we employ follows:

Ingredients: 1. Hydrogen peroxide U.S.P. 3 per cent. 2. Guaiac solution — 2 gms. powdered Guaiac dissolved in 120 cc. of 95 per cent alcohol (keeps indefinitely).

Method: 1 cc. Guaiac solution; 8 cc. hydrogen peroxide. A swab or applicator is dipped into the feces and it is added to this mixture, stirred well and allowed to stand for two minutes.

The amount of blood varies with the intensity of the color: light green, 1 plus; green, 2 plus; light blue, 3 plus; royal blue, 4 plus.

The only cure for gastro-intestinal cancer is early diagnosis and immediate surgery. The x-ray, of course, establishes the diagnosis in the vast majority of cases. Careful palpation of the abdomen is important; we have records of five cases in which this procedure was successful. The growth occurred in

the wall of the gut and protruded externally, so occult blood reaction and x-ray were negative. Two of the cases were located in the sigmoid flexure and three in the small intestine. All made complete recovery following surgery, and the pathologist found them all to be adeno-carcinoma.

The Post-Cholecystectomy Syndrome, Incidence, Etiology and Treatment

by
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DURHAM, N. C.

INTRODUCTION

DISEASE OF THE BILIARY TRACT is perhaps the commonest cause of upper abdominal discomfort. Graham and Cole (1) have stated that they believe that 24 per cent of the adult population have gallstones and that an equal number have cholecystitis without calculi. Mentzer (2) found evidence of bile tract infection in 66 per cent of 612 routine autopsies at the Mayo Clinic and in only 7 per cent had a primary diagnosis of cholecystitis been made. Many other authors note the incidence of gall stones to be between 20 and 25 per cent of adults (3, 4, 5, 6) and as high as 33 per cent (11, 12).

We shall not deal with the pathogenesis of biliary tract disease except to say that the idea that cholecystitis is caused primarily by chemical action seems to be gaining headway (7). But a few words as to current trends of treatment of cholecystitis and cholelithiasis are pertinent. Almost all the large surgical clinics in this country are agreed that once gall stones have been demonstrated either by x-ray or by the clinical course of the patient, cholecystectomy is the most advisable method of treatment (10, 12). Many authors advocate early surgical intervention in acute cholecystitis (13, 14, 23). Medical management of patients with biliary tract disease has not been wholly unsuccessful but early surgical treatment appears to yield a higher percentage of cures if the surgeon selects his cases carefully.

DEFINITION

The post-cholecystectomy syndrome can be defined as a recurrence of symptoms following removal of the gall bladder resembling or identical to those which existed prior to operation.

INCIDENCE

The results revealed by follow-up examination after cholecystectomy, especially in the group of patients with non-calculous cholecystitis, are rather discouraging (15, 16, 17, 18, 19, 20, 21, 22). The authors quote figures varying from 30 to 40 per cent of cholecystectomized patients complaining of some or all of the symptoms they had prior to operation. Most authors make the point that the greatest frequency of the post-cholecystectomy syndrome occurred in those

patients who had definite colic prior to operation and in whom functional disturbances were demonstrated by cholecystography but in whom the surgeon encountered either an absence of pathologic lesions in the gall bladder or the presence of a non-calculous cholecystitis. The syndrome was uncommon when a gall bladder filled with stones or a fibrotic functionless gall bladder and a dilated common duct was found.

CLINICAL MANIFESTATIONS

Dr. R. Colp (24) states: "the post-cholecystectomy syndrome may resemble cholecystitis and cholelithiasis in all their varied clinical manifestations and it may simulate many of the physical findings." The factors contributing to failure of cholecystectomy to relieve the patient's symptoms are many (19, 25), and the complaints which follow operation may be bizarre.

The acute symptoms, occasionally occurring even as early as during the convalescent period and most frequently noted within the first two years, may be initiated by excruciating, knife-like, colicky pains in both upper abdominal quadrants and often radiating through to the back and up under the shoulder blades and less commonly to the shoulders. Nausea and vomiting are frequent with these attacks, short periods of mild jaundice, pruritus and even intermittent fever and chills occur occasionally. Physical examination may reveal right upper quadrant soreness and a faint icteric tint to the sclerae. Doubilet (21) in the Surgical Clinic of the Mount Sinai Hospital in New York City, following 253 patients who had been operated upon for gall bladder disease for a period of one to seven years, notes an incidence of nearly 40 per cent who complained of postoperative symptoms. The majority were having acute attacks similar to those experienced prior to operation and these the author divided into two main types: 78 patients stated that the intense post prandial pain lasted from five minutes to two hours and occasionally radiated to the back; 24 patients complained of pain lasting from two to twenty-four hours radiating from the left upper quadrant to the shoulders and frequently accompanied by persistent abdominal soreness and in two cases an acute pancreatitis developed.

ANATOMY

In order to more easily appreciate the various theories as to the etiology of the post-cholecystectomy

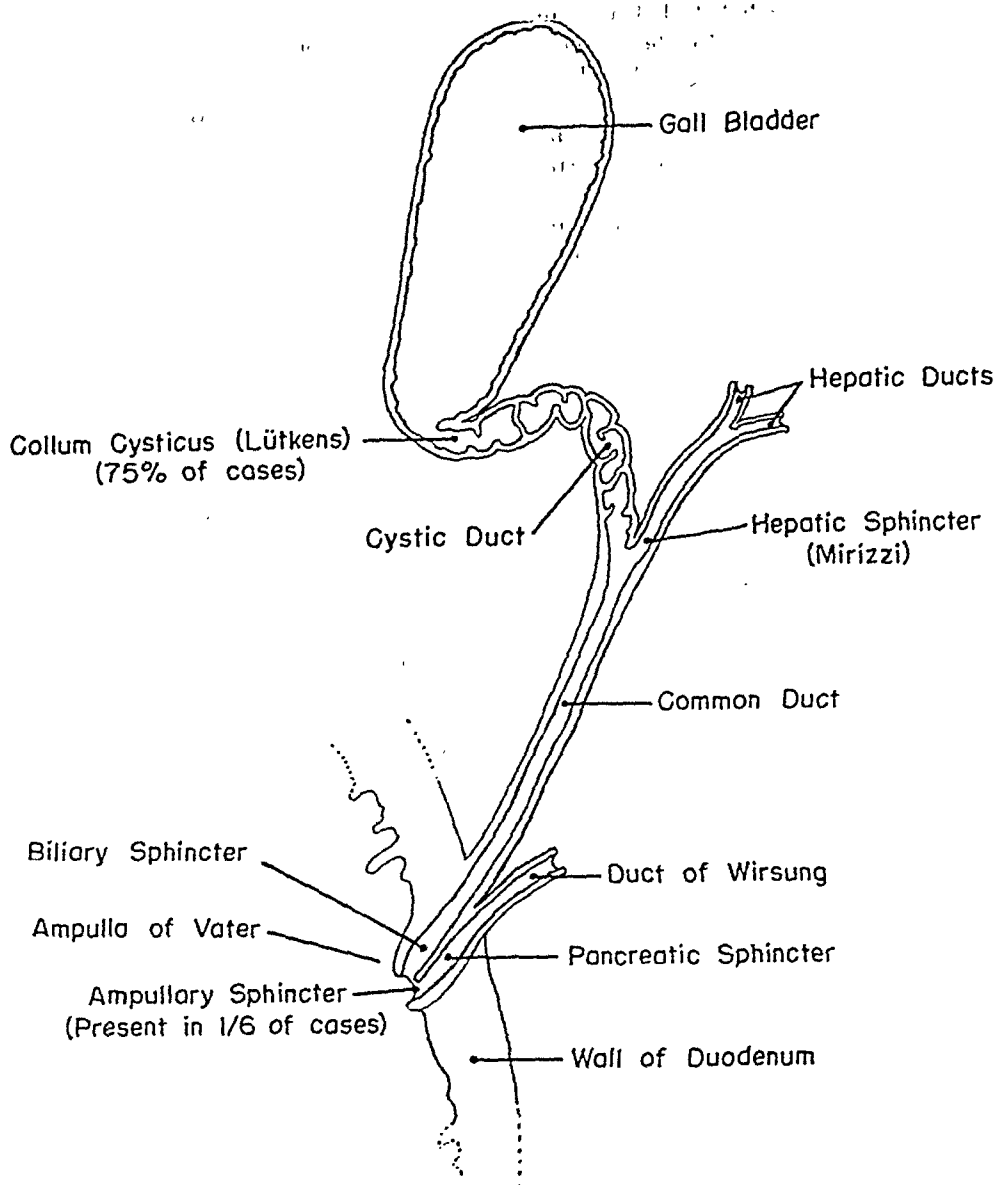


Figure 1. Location of the sphincters of the biliary and pancreatic ducts. Modified from "Postcholecystectomy Syndrome and its Treatment," by Ralph Colp (24).

syndrome a schematic diagram of the anatomy of the extra-hepatic biliary system is attached.

Hendrickson (26) in a study of the musculature of the extra-hepatic biliary systems in dogs, rabbits and man presented what is now regarded as the classic description of the musculature surrounding the lower end of the common bile duct. More recently Nuboer (27) demonstrated the relationship of the musculature of the lower end of the common bile duct to the musculature of the duodenum.

The embryology of this area has been investigated by Boyden and his associates (28) and they have demonstrated longitudinal fasciculi which probably serve to erect the papilla and aid in the ejection of bile, a sphincter of the pancreatic duct, a definite sphincter at the terminal end of the choledochus and in addition in one-sixth of their cases, a sphincter of the ampulla. Contraction of this latter sphincter converts the common bile duct and the duct of Wirsung into one canal with consequent reflux of bile

into the pancreas and pancreatic ferments into the common bile duct.

PHYSIOLOGY AND PHARMACOLOGY

Under normal circumstances the choledochal sphincter remains closed in-between meals and the normal gall bladder acts as a pressure regulating mechanism to keep the intra-ductal pressure in the extra-hepatic biliary system from exceeding the secretory pressure of the liver. The intermittent discharge of bile into the intestine is dependent, following humoral stimulation due to food in the stomach and duodenum, upon relaxation of the sphincter mechanism and simultaneous contraction of the intrinsic musculature of the gall bladder wall according to the Meltzer law of contrary or reciprocal innervation. Judd and Mann (29) demonstrated that the dilation of the common bile ducts which occurs in dogs following cholecystectomy does not occur when the choledochal sphincter is cut at operation. Potter and Mann (30) demon-

strated markedly increased intracholedochal pressure following cholecystectomy. It has also been shown that alkali placed in the duodenum increased and acid decreased the resistance of the common bile duct sphincter in dogs and that in human beings who had cholecystitis and duodenal ulcer, there was hypertrophy of the musculature of the sphincter (31). Kitakoji (32) has shown that drugs which excite parasympathetic nerves (muscarine, pilocarpine, physostigmine and especially acetylcholine) also stimulate the tone of the sphincter of Oddi both in vivo and in vitro and that drugs which paralyze the parasympathetic nerves (atropine, scopolamine) relax the sphincter of Oddi. He also demonstrated that morphine and nicotine cause a contraction of Oddi's muscle and that epinephrine and ergotamine tartrate produce slight if any change in the intra-biliary pressure.

ETIOLOGY

An explanation for the signs and symptoms of the post-cholecystectomy syndrome has been attributed by most authors studying the problem to dyskinesia of the sphincter mechanism (24, 33, 34, 35, 36, 37). This sphincter spasm may be stimulated either by local causes or by intra-biliary causes such as recurrent or residual calculi in the cystic or common duct, partial traumatic strictures of the choledochus, cholangitis or pancreatitis. Occasionally the spasm may be precipitated by psychic disturbances and by glandular dyscrasias and less commonly by a spastic colon.

Bergh and Layne (37), McGowan, Butsch and Walters (38), and Doubilet and Colp (39) have shown by manometric and lipoidal injections in the intubated common duct that there is increased resistance offered by the sphincter immediately postoperatively and marked spasm can be produced by certain drugs (morphine, codeine, dilaudid). Definite hypertrophy of the muscles of the ampulla has been observed following cholecystectomy by several authors (40, 41, 42). Gray and Sharpe (43), in reviewing 44 cases that were operated upon at the Mayo Clinic because of signs and symptoms of the post-cholecystectomy syndrome showed that in every case specimens of the cystic duct removed showed evidence of disease and in 35 cases or 79 per cent there was marked evidence of recent inflammation.

Several authors (22, 43) call attention to the fact that the signs and symptoms of disorders of other nearby tissues closely imitate and are frequently mistaken for disease of the extra-hepatic biliary tract, namely, acute intestinal pancreatitis. Angulation of the duodenum by attachment to the denuded gall bladder fossa may perhaps cause postoperative flatulence and vague epigastric distress. It is now well accepted that every case of cholecystitis and cholelithiasis is accompanied by a certain amount of hepatitis, cholangitis, pancreatitis and occasionally duodenitis. In some cases of long standing biliary tract disease, these secondary pathologic processes may have advanced to the point where they are irreversible and may give rise to symptoms following removal of the gall bladder.

These clinical and experimental observations all seem to point to the fact that biliary dyskinesia is

an important factor not merely in relation to the post-cholecystectomy syndrome but also in the pathogenesis of the original disease.

TREATMENT

The treatment of the post-cholecystectomy syndrome can be divided into two phases. The first is prevention. This includes the careful selection of patients since it has been shown that if stones are present operation affords permanent benefit in 80 to 95 per cent of cases (44, 45) and only slightly less satisfactory results are obtained following removal of non-calculous gall bladders in which there is evidence of advanced disease. The operation itself should be very carefully performed and the common duct explored only when there are excellent indications therefor (46).

However, when a patient develops the post-cholecystectomy syndrome following operation, careful evaluation and examination of the case is necessary prior to instituting therapy. It goes without saying that in those cases where there is evidence of anatomical deformity of the common duct resulting in increased intra-biliary pressure, bile stasis and hydro-hepatosis (47), a second operation is imperative in order to save the patient's life.

In those cases where the symptoms and signs can be attributed to biliary dyskinesia without anatomical deformity, medical management is indicated and in many cases is remarkably successful. Such antispasmodics as amyl nitrite, nitroglycerine and theophyllin in ethylenediamine (aminophyllin) have been shown to give relief from the acute episodes (35, 49, 50, 51). Although morphine, codeine and dilaudid have been shown to raise the intraductal biliary pressure, their central action alleviates pain and their use in certain cases appears justified. No reports on Demoral are available as yet but in one case in the author's experience it was by far the most effective medication used.

Dietary regulation is also useful. These patients should be advised to avoid heavy meals and eat small amounts of food at frequent intervals which would tend to provoke a constant rather than an intermittent flow of bile. Any type of rich or irritating food or excessive amounts of food and drink which might set up a duodenitis should be emphatically prohibited.

In cases where residual common duct stones are suspected or visualized by choledochography, a flushing regimen such as advised by Best (48) should be given a trial since he has shown that 25 per cent of common duct stones can be passed following this procedure.

Best's three day "Biliary Flush Regimen" is carried out as follows:

First Day:

1. Decholin or procholol — 3 tablets 3 times a day and at bedtime.
2. Nitroglycerine grains 1/100, 3 times a day before meals.
3. Magnesium Sulphate 2 drams before breakfast.

4. Pure cream 1 ounce before evening meal and at bedtime.

Second Day:

1. Decholin or procholol — 3 tablets 3 times a day and at bedtime.
2. Atropine grains 1/100 dissolved in a little water 3 times a day before meals.
3. Magnesium Sulphate 2 drams before breakfast.
4. Pure cream 1 ounce before evening meal and at bedtime.

Third Day:

1. Decholin or procholol — 3 tablets 3 times a day and at bedtime.
2. Nitroglycerine, grams 1/100, 3 times a day before meals.
3. Magnesium Sulphate 2 drams before breakfast.
4. Pure cream 1 ounce before evening meal and at bedtime.

Best places all his patients who have had a cholecystectomy with or without exploration of the com-

mon duct on this regimen starting on the eighth postoperative day and again on the fourteenth postoperative day and believes that the procedure is worthwhile in lowering the incidence of the post-cholecystectomy syndrome.

SUMMARY

The incidence of gall bladder disease in the general population is reviewed and the percentage of cases submitting to cholecystectomy who develop symptoms postoperatively is quoted from several of the larger surgical clinics in this country. The incidence appears to run between 30 and 40 per cent of cholecystectomized patients. The post-cholecystectomy syndrome is defined as a recurrence of symptoms following removal of the gall bladder resembling or identical with those which existed prior to operation.

The anatomy, physiology and pharmacology of the extra-hepatic biliary system are discussed and the various etiologies of the post-cholecystectomy syndrome are reviewed. A rational pharmacological basis for the treatment of biliary dyskinesia is presented.

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Pathogenesis and Treatment of Ulcerative Colitis with Extract of Hog Stomach

by

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THOSE SPECIFIC DISEASES producing ulcerative lesions of the colon, such as bacillary and amebic dysentery, and tuberculous enterocolitis, compose a small percentage of the cases presenting ulceration of the large intestine. On the other hand, by far the majority of cases with the characteristic diffuse ulcerative inflammation of the colon cannot yet be attributed to a known specific etiological agent. The term nonspecific or idiopathic ulcerative colitis has been ascribed to this clinical entity.

This discussion will concern itself with the idiopathic type of ulcerative colitis and the relationship of a protective substance or anti-proteolytic enzyme, in the prevention and treatment of nonspecific ulcerative colitis.

The work done has been entirely in vivo and conclusions drawn are from clinical observations.

It is not the purpose of this paper to disparage the established theories propounded by other observers and there is concurrence with Bockus (1) when he states, "This clinical syndrome is associated with a bacterial or toxic invasion of the bowel wall, conditioned by varying immunologic, allergic, nutritional and nervous phenomena."

Bacterial invasion of the intestinal mucosa has been demonstrated by many observers with such a remarkable multiplicity of micro-organisms as the specific offenders in the etiology of ulcerative colitis, that the constant inconsistency of a specifically predominant pathogen would appear indicative of its relative lack of establishment. Bagen (2) states, "The infection may be caused by one or more of several bacteria or animal parasites, in association with certain dietary and constitutional deficiencies, or by other conditions, some of them still unknown." On the other hand, the element of intraenteric infection cannot be disregarded as a contributing factor to the severity and chronicity of the disease.

Brown (3) expressed an interesting view in his analysis of the etiological void of specificity. "Is it not possible that the cause of the disease is to be found

not in the presence of a definite and specific infective agent, but rather in the absence of some protective substance or mechanism, of a something which normally inhibits the bacterial invasion of the intestinal wall, perhaps due to metabolic error, or endocrine disturbance, or lack of specific bacteriophage, or absence of some normal bactericidal substance in the intestinal mucosa."

The deduction is made that the intestinal mucosa is endowed with a substance, which for purposes of description the author designates as "an anti-proteolytic substance" whose function it is to protect the intestinal mucosa from autolysis by proteolytic enzymes which are contained in the intestinal contents. This anti-proteolytic factor appears to be most prolific in the stomach and small intestine, gradually decreasing in mucosal content in the large intestine and particularly in the descending colon and rectum.

Morrison (4) has culminated a series of investigative studies by several observers on the theoretical presence of a protective substance in the stomach and upper small intestine, by demonstrating clinically the prompt recovery in 10 patients with peptic ulcers by the administration of gastric juice from normal subjects. The remarkable response to this type of therapy would seem to substantiate the presence of a protective substance inherent in the gastric mucosa which would inhibit mucosal dissolution. Morrison (5) further demonstrated that a control group of dogs could be prevented from the development of cinchophen induced peptic ulcers by the feeding of a hog stomach preparation.

RATIONALE FOR EXTRACT OF HOG STOMACH

There is adequate reason to believe that the colon has likewise been imbued with a protective substance so that it, too, may inhibit self digestion when subjected to contact with proteolytic enzymatic activity. Biologic endowments are usually consistent with the physiological chemistry at hand, and since the colon is not an organ in which primary digestion takes

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place, the ratio of this anti-proteolytic factor is likewise apparently less available than in the stomach and small bowel. However, when gastro-intestinal hypermotility exists, proteolytic enzymes are more active and abundant in the colon than under normal circumstances, with the resultant exhaustion of the anti-enzymatic substance so as to allow proteolytic dissolution of the colonic mucosa.

The presence of proteolytic enzymes in feces has been well established. Howell (6) states that the contents in the large intestine contain digestive enzymes received in the duodenum, and that the digestive and absorptive processes no doubt continue as in the small intestine. Bockus (7) in discussing the secretory function of the large intestine states that the normal presence of mucus may have a local detoxifying function rendering certain harmful enzymatic substances inert. This further infers from his observations that the large intestine does contain harmful enzymatic activity. Hawk and Bergeim (8) state that the nitrogen in feces exists principally in the form of bacteria, unabsorbed intestinal secretions and digestive juices. Bacon (9) states that the residual mass of material in the large intestine is composed of food residues, the remains of intestinal and digestive secretions.

By definition, enzymes are substances which have a catalyst like action which increase the velocity of chemical reaction without themselves being changed or used up during the process. Starling (10) concluded that minimal quantities of enzyme can induce chemical changes, involving almost unlimited quantities of other substances. The only result of increasing the quantity of enzyme being to quicken the rate of change. This would emphasize that enzymes present in the large bowel have not lost their activity after engaging in hydrolysis.

The element of hydrogen ion concentration in the colon does not preclude the activity of proteolytic enzymes in the colon. Pepsin may be inhibited by the neutral or alkaline reaction of the colon, but trypsin and erepsin are not in an unfavorable pH. It has been demonstrated that pepsin is not essential to proteolytic hydrolysis. On the other hand, tissue autolysis is explained by Harrow and Sherwin (11) on the basis of pH variation: "It is seen that normal tissue is saved from autolysis by the preservation of its normal hydrogen ion concentration. If, however, acid forms more rapidly than can be normally taken care of, the primary proteolytic action is favored and tissue breakdown occurs. The primary cleavage products are broken down further by second enzyme which is effective in a slightly alkaline medium, and therefore can act even if the pH is brought back to normal. If inhibitory substances are present in sufficient amounts, autolysis will, of course, not occur."

Further, putrefactive bacteria in the large intestine complete proteolytic digestion to the stage of amino acids and their end products. Buchner succeeded in extracting enzymes from lactic acid producing bacteria and acetic acid producing bacteria, which are capable of giving the same reaction as living bacteria. His studies clearly indicate that there is no essential

difference between the activity of living and non-living ferments (pepsin, trypsin, erepsin). He further stated that these acid producing bacteria probably produce their effects not by virtue of their specific life metabolism, but by the manufacture, within their substance, of specific enzymes. Therefore, it can be concluded that the intestinal mucosa may be besieged by the true exogenous proteolytic enzymes and their action enhanced by the living ferments found in the intestinal flora.

GASTRO-INTESTINAL HYPERMOTILITY

Gastro-intestinal enzymes are basically hydrolytic enzymes producing hydrolysis of the substrate by the inter-action of water. Fecal composition in the patient with gastro-intestinal irritability, and resultant diarrhea, is usually liquid in character throughout its transit through the large intestine and rectum, thus enhancing the perpetuation of proteolytic enzymes in the distal colon. By the same token, whenever hypermotility of the gastro-intestinal tract exists, pepsin from the stomach, trypsin and erepsin from the small bowel are shunted into the large intestine in a fraction of the usual emptying time with the result that active proteolytic enzymes are in contact with the colonic mucosa before they have, at least in part, been reabsorbed.

The deduction by Rivers (12) in reporting the work of Mann and Kawamura seems to be well founded. In an attempt to determine the defense mechanism of the duodenal mucosa, they resected the duodenum in experimental animals with a resultant gastro-jejunos-tomy. In 20 per cent of the animals a marginal ulcer promptly developed, indicating the duodenum has a protective mechanism to acid chyme not possessed by the jejunum. He concludes that perhaps the cells of the duodenal mucosa secrete a protective substance which alters the gastric chemism to curtail its eroding properties. It is our belief that when degrees of hydrolysis are not completed in normal physiological stages through each segment, such as in hypermotility, the colon is deprived of some of the anti-proteolytic activity which has been proved to exist in the duodenum.

It is particularly to this type of mechanism that reference is made, when it is suggested that the protective or anti-enzyme contained in mucosal cells is inadequate to cope with autolysis in face of the abundant and yet viable proteolytic enzymes; compared with the normal physiology of the intestinal contents, undergoing absorption and a comparative dehydration before its arrival into the sigmoid and rectum.

Still another factor in the predisposition to mucosal autolysis of the colon can be based on the findings of Cannon (13) who has shown that the composition of the secretion of pancreatic juice varies with the character of the food, and indeed shows an adaptation to the character of the food. The secretion caused by protein food is essentially rich in trypsin. Therefore, patients on consistently high protein diets, would be found with a fecal residuum of a high ratio of proteolytic enzymes, thus upsetting the enzyme anti-enzyme balance.

Again referring to the work of Starling (14), he found that the velocity of enzyme action is accelerated by increasing the concentration of the substrate. Thus a preponderant protein intake would increase the concentration and velocity of proteolytic enzymes, with the end result, that the anti-proteolytic substance would be predisposed to exhaustion.

The key to the pathogenesis of ulcerative colitis is aptly expressed by Winkelstein and Schwartzman (15) who concede that there is lack of knowledge of the primary etiologic agent in most cases of ulcerative colitis, but state that once the mucosal barrier is broken, secondary infection due to a variety of bowel organisms contributes to the serious damage of the disease. Likewise, Mones and Sanjuan (16) concluded that in ulcerative colitis there exists some principle which gives pathogenic power to bacteria which are ordinarily non-pathogenic. This supposed facultative power is believed by the author to be due to the relative dissolution of the intestinal mucosa by proteolytic enzymes, destroying its anti-bacterial property.

SUMMARY OF PATHOGENESIS

The evolution of idiopathic ulcerative colitis would seem to revolve about the following predominant factors predisposing to mucosal autolysis:

1. By physiological implication, the anti-proteolytic substance exists in decreasing amounts through the rectum and colon.

2. Gastro-intestinal hypermotility, whether it be neurogenic, psychogenic, gastrogenous, local irritation of the intestinal mucosa from end-products of proteolytic cleavage, or due to other factors postulated as the etiology of hypermotility, the end result is the same. That is the premature presence of substrate in the large bowel, with the result of active digestion in a locus not intended for this function.

3. The secretion of succus entericus is usually augmented by diarrheic states, thus increasing the concentration of proteolytic enzymes. This increased concentration effects the velocity of enzymatic activity, requiring an anti-proteolytic action greater than normal. On the contrary, anti-enzymatic activity will eventually exhaust itself when exaggerated demands for anti-proteolytic protection are constantly placed upon it.

4. Since pancreatic juice shows an adaptation to the character of the food, a persistently high protein diet will result in fecal residue high in proteolytic enzymes. This again means increased velocity of enzymatic activity.

5. An inherently low proteolytic threshold with a low anti-proteolytic tolerance. Thus even in non-diarrheal states, mucosal dissolution may eventuate as the result of a feeble anti-proteolytic substance response.

6. A high putrefactive flora is a contributing mechanism by its secondary proteolytic effect.

7. Mucosal dissolution contributes in destroying the defense mechanism to bacterial invasion and produces a desirable medium for pathogenic activity, thus add-

ing to the severity or chronicity of the disease.

MODE OF THERAPY

The principle of therapy in idiopathic ulcerative colitis with dessicated extract of hog stomach, is concluded to be the presence of an anti-proteolytic substance contained in the extract. It is apparently absorbed and effects its anti-enzymatic property by its deposition in the mucosa of the intestinal tract in the manner of an endo-enzyme. It should be mentioned that dessicated extract of hog stomach also has the property of an anti-anemic, which, while it is supportive therapy, there is doubt that it influences the restoration of the colonic mucosa in any specific fashion.

The author first used this approach of dessicated extract of hog stomach three years ago, since the theory of mucosal dissolution by proteolytic enzymes seemed to be a very specific and logical mode of pathogenesis of ulcerating lesions of the colon. At the outset, this approach was used to supplement therapy in resistant cases, that is, those which did not respond to the usual methods. It was evident by sigmoidoscopic examination after two to four weeks of therapy that edema, inflammation, intraluminal bleeding and the erosion of the mucosa were decidedly less.

No attempt was made to exploit the apparent efficacy of the preparation to the patient, so as to in no way influence the psychological reaction to therapy. Therefore, no mention was made to patients of any unusual expectancy from this medication but simply prescribed without comment, and awaited voluntary remarks from the patients regarding their progress.

These patients ranged in age from 18 to 60, and the duration of symptoms from two months to five years. Five cases were those who had a previous history of episodes of the disease and who came under our care because of a recurrence of symptoms. Each case was thoroughly interrogated and adequately studied by laboratory and sigmoidoscopic examination to definitely establish the diagnosis of idiopathic ulcerative colitis.

While dessicated extract of hog stomach was used in a larger number of cases than will be discussed here, this report is confined to those cases in which it constituted the principal method of therapy. A total of 15 cases were studied, presenting the classical picture of idiopathic ulcerative colitis.

The preparation administered in this series of cases was a dessicated extract derived from fresh hog stomach tissue. Forty grams of powdered stomach is represented in four heaping tablespoonfuls of the preparation. The dosage varied from 30 to 60 grams daily, or 3 to 6 heaping tablespoonfuls. It was administered in divided doses before meals. The variance in dosage depended upon the severity of the case. An average dose of 40 grams was used. In the protracted and fulminating cases, the initial dose was always 60 grams daily, gradually reduced as amelioration of symptoms and endoscopic improvement resulted. At least six ounces of liquid should be taken with or immediately following its administration. Inasmuch as the substance is insoluble and

in some cases not always palatable, it was necessary to give it at the first part of the meal.

After improvement a maintenance dose of usually 10 grams three times daily, was continued for a period of one to four months. The dosage was not reduced until adequate resolution was evident by endoscopic visualization. Each case was sigmoidoscoped at weekly intervals during the active phase, then once monthly. Patients were not advised to prepare with enemata until the disease was quiescent and formed feces obscured visualization.

It has occurred to the author that the combination of oral and local treatment would be more effective than either one singularly. Therefore, at the time of this writing, insufflation of extract of hog stomach directly into the rectum and sigmoid by means of the sigmoidoscope and a long rubber catheter is being employed. Since this method of approach has just been instituted, a report of its efficacy cannot be made at this time.

RESULTS OF THERAPY

As was stated at the outset, secondary invasion by micro-organisms of the intestinal flora aggravated the severity and course. Therefore, in some of the acute fulminating cases or the severe chronic continuous type, it was necessary to supplement treatment with Sulfonamide medication by mouth. This was further established by a test period of one month with dessicated extract of hog stomach before Sulfonamide treatment was started.

It was noted that in only two of the four cases in which Sulfaguanidine or Sulfasuxidine was necessary, that there was any direct visual change in the character of the ulcerative lesions. However, in three of the four cases, diarrhea, abdominal cramps and sanguino-purulent exudate decreased. This was most pronounced in an adult female with an established history of five years duration. Sulfa medication was omitted at this time and dessicated extract of hog stomach was then resumed in maximum dosage with resultant clinical and endoscopic recovery.

In the remaining eleven cases, the results were remarkable following one to four weeks of administration of dessicated extract of hog stomach, in which, by endoscopic visualization, edema, inflammation, spasm and ulceration had definitely subsided.

In eight cases, at the end of one month, there was no evidence of inflammation or ulceration, and in seven cases, two to three months of therapy was ne-

cessary before the mucosa approached normality.

It was found that by using a maintenance dose after resolution, the results were more satisfactory, for in four cases that did not abide by this suggestion, a relapse occurred from one to five months after discontinuing the medication. However, when medication was resumed at therapeutic dosage, the symptoms and sigmoidoscopic picture soon returned to normal.

In three cases, when there was no evidence of inflammation or ulceration, moderate diarrhea persisted, reverting back to the initial stage of colonic hypermotility, but should not be classified as ulcerative colitis since the pathology of the rectal and sigmoidal mucosa was absent. This benign diarrhea apparently has as its background emotional tension or anxiety and is psychosomatic in origin. This was particularly evident in one patient who had very strong guilt feelings and self-reproach.

CONCLUSIONS

1. With few specific exceptions, as amebic and bacillary dysentery, and tuberculous enterocolitis, ulcerative colitis is a non-specific disease.

2. Proteolytic enzymes are present in the colon and rectum. Gastro-intestinal hypermotility enhances the delivery of active proteolytic enzymes into the colon, thus predisposing the colonic mucosa to autolysis. It is presumed that the colon normally contains an anti-proteolytic or protective substance to inhibit dissolution of the mucosa. This anti-proteolytic substance seems to be particularly deficient in the descending colon and rectum under the mentioned circumstances, thus upsetting the proteolytic, anti-proteolytic enzymatic balance predisposing the individual to degrees of mucosal autolysis.

3. Dessicated extract of hog stomach appears to contain this anti-proteolytic substance.

4. Fifteen cases of idiopathic ulcerative colitis are herein reported in which extract of hog stomach was administered. Remarkable restoration of an intact mucosa resulted. Four cases required Sulfonamide therapy for secondary infections. In four cases it was necessary to repeat administration of the medication as relapses occurred after its omission.

5. Dessicated extract of hog stomach appears to be promising as a more specific approach, and its use in a greater number of cases and its observation over an adequate period of time, will shed more light on its specificity of action.

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A Procedure Helping the X-Ray Examination of the Gastro-Esophageal Segment *

by
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MANY METHODS have been devised for the roentgenologic study of the esophagus and stomach. Sometimes, it is rather difficult to say if a lesion or shadow belongs to the lower end of the esophagus, to the abdominal esophagus or to the gastric fundus.

The ordinary X-ray examination includes fluoroscopy and roentgenography with the patient in different positions: upright, Trendelenburg, supine, prone (1, 2). The special procedures commonly used for the study of the esophagus may be numerated as follows: Valsalva test, pressure on the abdomen to overcome the resistance of the diaphragmatic "pinch-cock" (Templeton).

Martin and Rogers (3) introduced an ingenious technic by inflating soft rubber balloons either in the cardiac portion of the esophagus or in the stomach itself; on the silhouette of their roentgenograms, a complete circular constriction in the lower third of the stomach was observed, in some instances.

In the hands of Jutras (4) and W. F. Gruber (5), the inflation of the balloon is followed by swallowing of opaque mixture and by the registration of the fluoroscopic findings on roentgenograms. Golden (6) has already employed the Millers-Abbot tube, for small intestine examination.

Having been called to help in making clearer diagnosis for two cases, the author found the Levin tube a valued diagnostic aid in both conditions: epiphrenic diverticulum and hiatal herniation of the stomach.

The technic does not eliminate the esophagoscopy examination (7, 8, 9, 10, 11, 12, 13, 14).

PRINCIPLES AND TECHNIC

Almost every lesion involving the supra or infra-diaphragmatic portion of the esophagus is associated with cardiospasm. In many instances, we found out that the spasmodic contractions become more active while esophageal bougie or Levin tube is passed through the hiatus esophagus; somewhat of a barrier between the stomach and the esophagus is taking place.

During the filling of the stomach with the opaque mixture through the Levin tube, the spasmodic hiatal stricture prevents the regurgitations of the barium milk upward into the esophagus.

This phenomenon was applied to the following il-

lustrative cases, the patient having been placed in different positions upon the fluoroscopic table, even in the Trendelenburg position.

We are indebted to Dr. P. Brodeur and Dr. L. P. Belisle from the X-ray Department to have made possible the realization of this new method.

TECHNIC

A Levin tube is introduced into one naris and pushed into the hypopharynx. With mouth closed, the patient is asked to swallow; in the meantime, the operator introduces the tube deeper and deeper down into the stomach.

When too great a resistance exists at the hiatus, some pressure on the abdomen may relax the diaphragm.

Sometimes the spasm asks for dilatation with esophageal bougie under esophagoscopy guidance, in order to allow the introduction of the Levin tube into the stomach, with the aid of an esophagoscopy forceps.

This handling may be done in the bronchoscopic operating room or in the X-ray dark room.

Once the tube penetrates the stomach cavity, the manœuvres must be performed under fluoroscopic guidance.

With a 50 cc. syringe, one inflates the stomach and observes its contours, particularly the fundus in contact with the diaphragm, so that a vacuolar hernial shadow may be visualized if any exists.

The second step consists in instilling barium mixture into the stomach, a small amount at a time in order to have a better spreading on the surface of the stomach. During the filling, fluoroscopic study and filming are taken while the patient is placed in different positions (1, 2).

REPORT OF TWO CASES

FIRST CASE

Mr. G. B. . . , 66 years of age, enters Notre Dame Hospital on November 7, 1944, for dysphagia and heart trouble. He was under Dr. Roger Dufresne's medical care. His chief symptoms may be summarized: retroxiphoid pain, dysphagia cough, regurgitations, no bleeding, loss of weight. Wassermann was positive.

Five months previously, the following diagnosis was made by an X-ray man and a bronchoscopist: "Achalasia of the lower end of the esophagus with dilatation and retrograd stasis, probably an ulcerative esophagitis."

On November 11, Dr. Dufresne received this report from Dr. Belisle: "At the lower end of the esophagus exists just above the cardia a dilatation which looks like a para-esophageal small hernia of the stomach. There is no dilatation of the esophagus. An aneurism of the aortic arch is present" (Fig. 1, a, b).

On November 22, our endoscopic examination revealed these findings: "Partial stenosis of the left main bron-

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Submitted May 1, 1947.

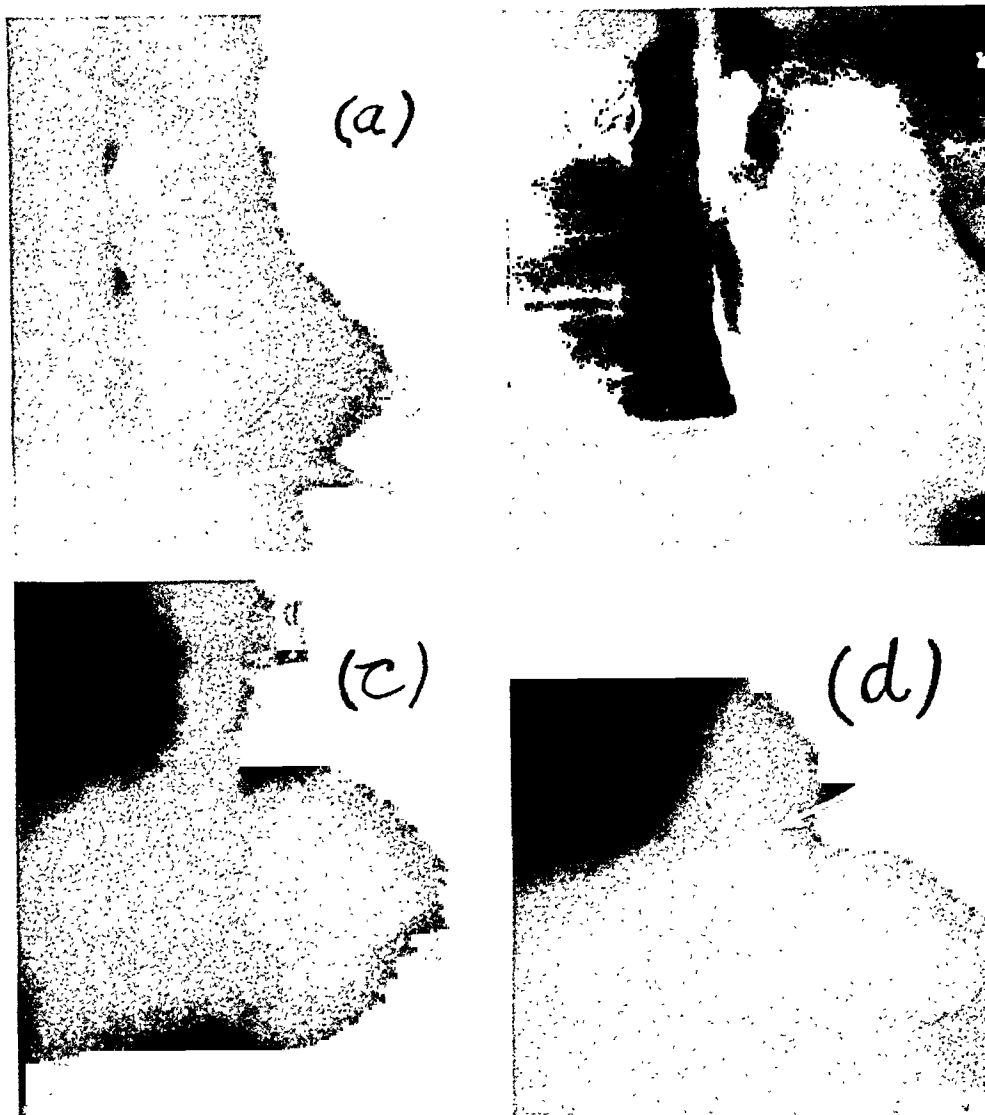


Figure 1. — The pocket (arrow) filled with air (a) and barium mixture (b) appeared to the radiologist, as a herniation of the stomach. The Levin tube method proves that there is no solution of continuity of the gastric wall along the diaphragm; consequently no typical hernia exists (c). Once the distal end of the tube is pulled just above the hiatus, the pocket becomes filled with opaque mixture (d). The epiphrenic diverticulum appears evident.

chus by compression due to the aorta. The lower end of the esophagus shows normal mucous membrane. But just above the hiatus with a spasmodic stenosis, on the left wall of the lumen, bubbles appear during expiration; they come from a depression which seems an orifice connected with a pouch."

Our preliminary diagnosis was: "Cardiospasm associated to an epiphrenic left diverticulum of the lower end of the esophagus."

To have our diagnosis more accurate, we imagined the use of a Levin tube for the filling of the stomach with opaque mixture.

On November 30, an esophagoscopy was done and the hiatus dilated with a 16 Fr. esophageal bougie; through the scope, a Levin tube was pushed into the stomach. Five days later, under fluoroscopic guidance, the filling of the gastric cavity did neither show any solution of continuity nor diaphragmatic hernia of the fundus. As soon as the Levin tube was drawn up just above the cardia, we poured in the tube some opaque mixture which enters a pocket evidently looking like an epiphrenic diverticulum. No reflux upward from the stomach was observed.

We might say our procedure was of a definite diagnostic value in this case.

SECOND CASE

Mr. A. M. . . , 35 years old, on March 21, 1945, saw his doctor, Dr. C. E. Grignon, and told him the following history. During the last five years, he had been complaining of epigastric pain while in bed; in the right lateral decubitus position, the pain was greater and pyrosis present; while on the left side, no pain, no pyrosis but eructations and rumbles left him restless at night.

On March 8, in a first report, Dr. Brodeur, roentgenologist, concluded: "A diaphragmatic hernia is present, maybe a so-called short esophagus with ulcerations: this hernia is reductible while the patient is in the upright position, so that a few roentgenograms show the abdominal portion of the esophagus in a normal position" (Fig. 3, a, b).

We may summarize our esophagoscopy examination as follows: "The esophageal mucosa, 30 cms. below the upper teeth, shows longitudinal ulcerative white trails along the longitudinal folds. At this level, the



Figure 2. — This shadow (a) looks like a hiatal hernia of the stomach which might be a short esophagus. The roentgenogram (b) taken in upright position, indicates dilatation of the esophageal lumen without the stricture particular to short esophagus (further details in Figures 3 and 4).

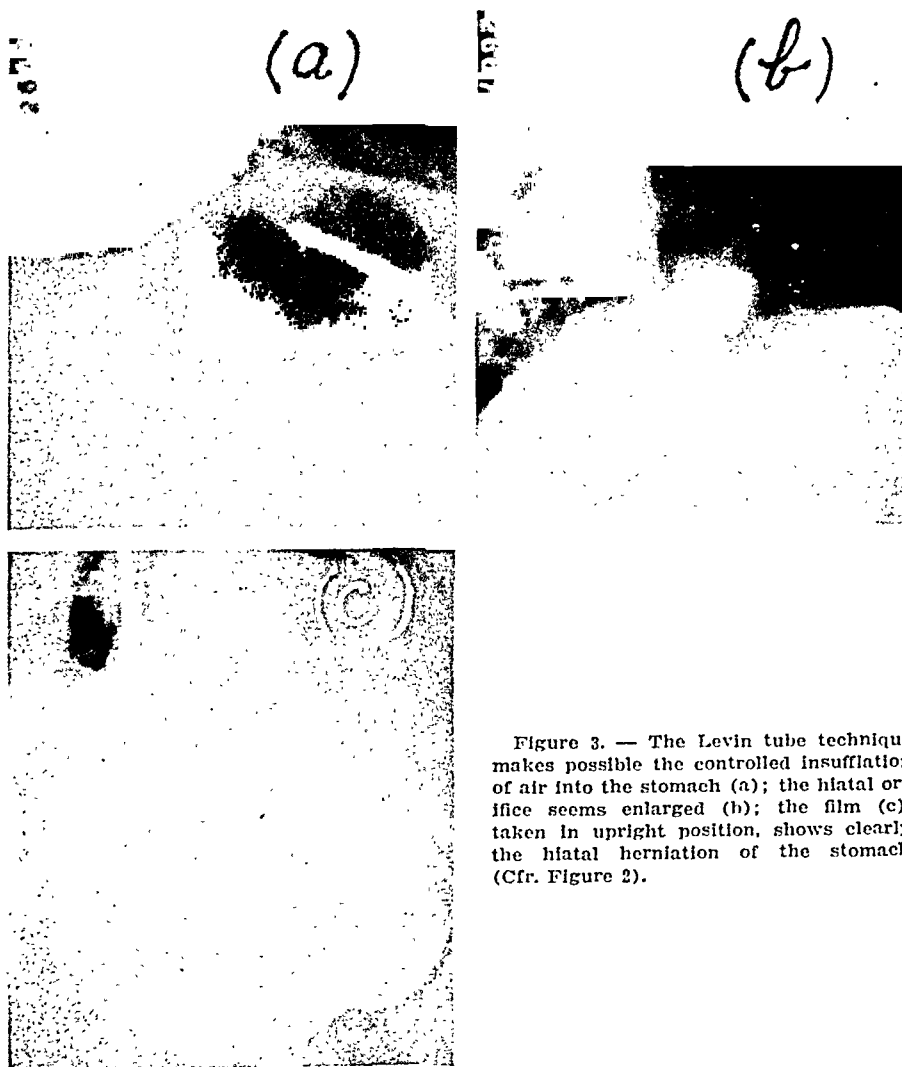
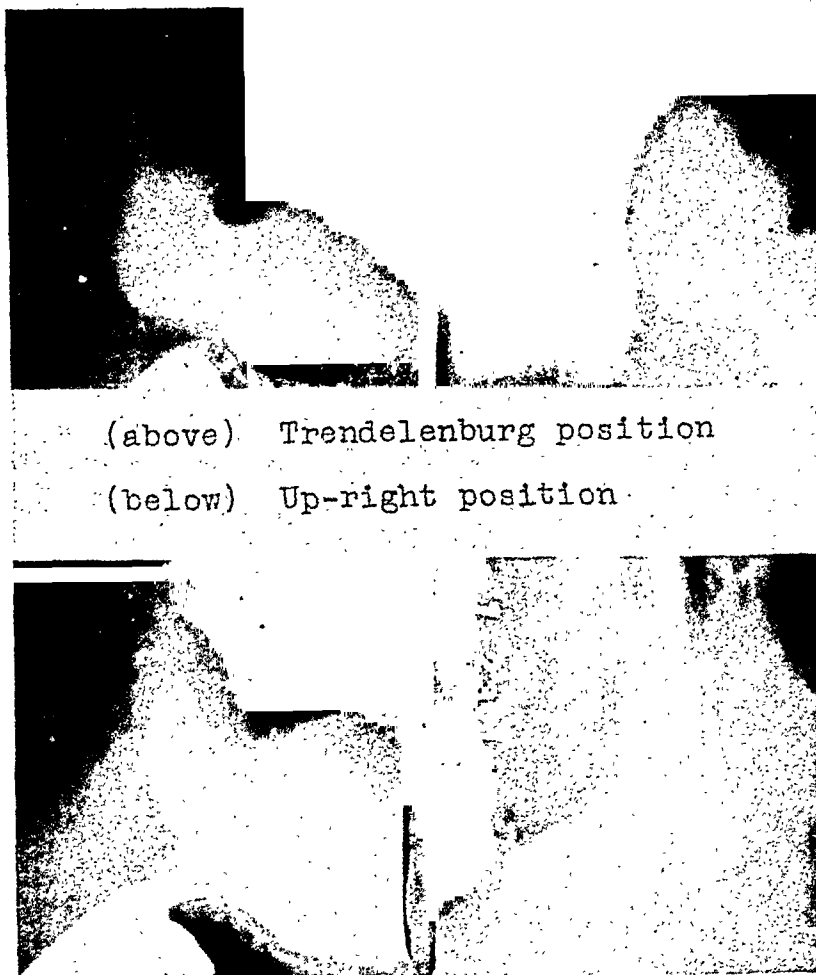


Figure 3. — The Levin tube technique makes possible the controlled insufflation of air into the stomach (a); the hiatal orifice seems enlarged (b); the film (c), taken in upright position, shows clearly the hiatal herniation of the stomach (Cfr. Figure 2).



(above) Trendelenburg position

(below) Up-right position

Figure 4. — Since the esophagoscopy examination, the patient is no longer complaining of first symptoms; he rather has regular life and sleeping. The films recently taken, i. e., two years after those of Figure 3, show the pathologic contours still present, but the hiatal hernia looks easily and spontaneously reductible (Cfr Figures 2 and 3).

lumen is conic with the base upward; but the apex is still much above the diaphragmatic hiatus, below this stenosis, the mucosa is of gastric appearance. We feel the local condition responds to a hiatal hernia with short esophagus."

On April 4, Dr. Brodeur and I employed the Levin tube method: air insufflation and barium instillation into the stomach. The wide aerogastria did not induce any intrathoracic air pocket (Fig. 4). The patterns of the barium suspension showed more accurately the diagnosis of hiatal hernia of the stomach.

The dilatation performed at the esophagoscopy examination had relieved the patient of his complaints.

The clinical course proved that no short esophagus was associated with the hiatal herniation.

Here again one must say the Levin tube technic was a real aid for the differential diagnosis.

SUMMARY

Sometimes a pathologic pouch around the diaphragmatic hiatus cannot be exactly interpreted. Even the esophagoscopy examination is not conclusive. The use of a Levin tube for inflating and filling the stomach was a helpful procedure in making a sure differential diagnosis.

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Sodium Ascorbate in the Treatment of Allergic Disturbances

The Role of the Adrenal Cortical Hormone-Sodium-Vitamin C

by

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FOLLOWING AN EARLIER WORK on high dosage Vitamin C in allergy, it became apparent that a very significant role was played by the inorganic ion sodium when used as the salt of Vitamin C. By a detailed microscopic study of bronchial reactions it was demonstrated that Vitamin C had a definite antihistamine effect, or an epinephrine potentiality effect. In practical application it was possible to demonstrate that daily dosages between 1000 mg. to 2000 mg. of Vitamin C afforded in many cases considerable relief from allergic manifestations and in some cases even striking and dramatic improvement. There remained however a group of cases that were either not benefited or were only moderately improved.

Analysis of these latter cases showed as a rule concomitant infection with a history of repeated colds, or bronchial infection. They were of the type usually classified as individuals with a lowered resistance to infection.

When, as a result of my technical advance in Vitamin C research there was made commercially available the dry sodium salt of Vitamin C an investigation of its use in allergy was undertaken. Originally, it was believed that the chief advantage of the sodium salt would be in the fact that it was a neutral form of Vitamin C, since the high dosage of Vitamin C entailed a daily amount of 1.5 gram to 2 grams, and gastric irritation was experienced frequently. Another factor was the continued and at times undesirable increase in ingested acid.

While the kidney has the power to form ammonia for the purpose of neutralizing an acid urine, it can also produce acid as $\text{Na H}_2\text{PO}_4$ and also as free organic acid, provided the pH does not fall much lower than 4.0. When, however, large amounts of acid are introduced into or produced in the body the ammonia producing mechanism of the kidney cannot suffice and the sodium bicarbonate of the blood is depleted for the purpose of neutralizing the acid. The CO_2 is exhaled by the lungs and the sodium salt of the acid appears in the urine; hydrochloric acid, for example, is excreted as sodium chloride, sulphuric acid as sodium sulphate.

If acid be fed and base is withheld from the diet for some days, sodium salts are excreted at first and little extra potassium, calcium or magnesium appears. Gradually, as the requirement for base becomes more insistent abnormally large amounts of

potassium are excreted. The body manifestly resists potassium loss as long as possible; probably because potassium and magnesium are essential to cell function in a more direct way than sodium. The depression of sodium levels may play an important role in kidney blockage from drugs of the sulfa group. Thus the availability of sodium ascorbate gave us an important agent in acid base equilibrium.

Analysis of blood and tissues shows a remarkable difference in distribution of cations — according to Holmes.

Cation	mg. in 100 gms. of plasma	mg. in 100 gms. of muscle
Sodium	138.0	60.
Potassium	18.0	360.
Calcium	10.5	10.0
Magnesium	2.7	23.

It is apparent that tissue cells contain far more potassium than sodium and that sodium loss would come first.

Sodium, however, plays a vital role in connection with the normal metabolism of the adrenal cortex. One could consider that the adrenal cortical hormone, sodium and Vitamin C, bear a reciprocal relationship to each other. It is, therefore, not surprising to find that the cortical hormone protected against histamine shock similar to that of Vitamin C. Thus Ingle showed the protective effect of fragments of viable cortical tissue and of transplants of cortical tissue on the resistance of suprarenalectomized rats to histamine shock. These observations were confirmed by Wyman and Tum Suden. They also showed that the increased susceptibility of the rat to histamine after suprarenalectomy depends on the loss both of medullary and cortical function.

However, Perla and Marmorstan found that when cortin is administered during the early period of insufficiency, the resistance of suprarenalectomized animals is raised to a striking degree, whereas when epinephrin is similarly administered, the resistance is raised only to a slight degree. By the administration of cortin, they were able to raise the resistance of suprarenalectomized rats to histamine almost to the normal level.

A further interesting point arose when the cortical hormone was used in experimental infections. Scott, Bradford, Hartman and McCoy determined the

effect of the cortical hormone on the resistance of normal animals. Three types of intoxication were used; diphtheria toxin in the guinea pig, trypanosome equiperdum infection in the rat and pneumococcus infection in the mouse. No protection was obtained against one minimum lethal dose of toxin by administration of cortical extract in amounts of one and one-half cc. Injections of cortin were commenced after the injection of diphtheria toxin. Similar results were produced in the other infections. All the mice were dead within 32 hours. The administration of cortical extract did not produce any appreciable survival period of white mice following infection with pneumococcus.

Zwemer and Jungeblut showed some protection by the injection of cortical extract in normal guinea pigs against a minimum lethal dose of diphtheria toxin. On the whole the results were not striking although apparently under certain conditions the administration of a large dose of a cortical extract may protect the guinea pig against more than one M.L.D. of diphtheria toxin.

Thaddeus, however, observed definitely beneficial effects of injection of cortical hormone when combined with Vitamin C on the resistance of guinea pigs to diphtheria. Cosentino likewise reported favorable results in rabbits infected intraperitoneally with cultures of staphylococcus aureus by the use of Vitamin C and adrenal cortical hormone.

Heuer and Andrus have reported that cortical extract has a protective action against the shock produced by intravenous injection of intestinal loop fluid into dogs. Meek also noted beneficial effects from the administration of cortin to dogs suffering from shock following intestinal distension. There is the further observation of Wolfram and Zwemer in the amelioration of anaphylactic shock in guinea pigs by the prior administration of cortin.

In an earlier paper on Histamine-Adrenalin Balance in Allergy, I pointed out that shock of the most varied sort ranging from severe burns and trauma to poisonings have a common histamine reaction directly analogous to nasal allergy and asthma.

The interrelationship of the adrenal cortical hormone to Vitamin C and Sodium led to the hypothesis that this triad of substances may play a basic role in allergy and that the deficiency of any one or more of these elements would predispose to allergic reactions. The Pottengers had already treated a group of 50 allergic children suffering with asthma by means of whole adrenal gland and a high salt intake. In addition a diet rich in vitamins and minerals was given. Improvement was observed in 84 per cent of the patients.

It now remained to observe the isolated effect of sodium ascorbate. Marine and Baumann had found that daily intraperitoneal injections of various sodium salts such as isotonic sodium chloride, sodium acetate,

Ringers solution, prolonged the lives of suprarenal-ectomized rats to almost three times those of the untreated suprarenalectomized controls. They pointed out the specific value of sodium salts in maintaining the life of the animal. Similar findings were observed by Stewart and Rogoff, although they found that salt solution could not be used as a substitute for cortical hormone. Loeb and his coworkers extended the studies and from their work suggested that suprarenal insufficiency was associated with a primary loss of sodium through the kidney. Harrop and his associates were able to maintain bilaterally suprarenalectomized dogs for as long a period as five months without the use of any suprarenal gland preparation or extract by the administration of sodium chloride and sodium bicarbonate alone. Withdrawal of the salt then produced typical suprarenal insufficiency. It has been shown by Zwemer and Truszkowski that a drop in sodium concentration in the blood is associated with a significant rise in the Potassium concentration. The production of such an electrolyte disturbance as suggested by Gilman and Yannet decreases the natural resistance of unoperated rats to histamine poisoning (Perla and Sandberg).

The interrelationship of histamine sensitivity to adrenal cortical insufficiency and sodium and Vitamin C led to the hypothesis that nasal allergy and asthma may be precipitated by an imbalance of the triad cortical hormone-Sodium-Vitamin C. In view of the reciprocal capacity that exists between them, a study was undertaken on the effect of sodium ascorbate, particularly in those allergic cases that were somewhat refractory to high dosage ascorbic acid. The beneficial effects were strikingly greater than ascorbic acid itself. There was in addition marked freedom from gastric irritation with the use of 2 grams daily. Increased diuresis was noted almost as a rule. Several of the cases were intractable asthmatics who had been refractory to almost all forms of therapy but have remained free from asthma in a fairly continuous level of sodium ascorbate. The seasonal hay fever cases did particularly well.

In reviewing the results obtained with ascorbic acid, calcium ascorbate and sodium ascorbate, it would appear that the inorganic ion plays a very important role. It would seem that many factors influence histamine sensitivity. Among these are enzymatic reactions and toxic factors that are favorably influenced by calcium ion whereas another important group may be related to adrenal cortical insufficiency and be strikingly helped by the sodium ion. In both cases the inorganic ion as the salt of ascorbic acid represent a very desirable form of therapy in allergy.

The use of the sodium salt of ascorbic acid may also play an important role in other conditions such as urinary lithiasis when the solvent action of the ascorbate on carbonates is utilized as well as the solubilizing effect of the sodium ion.

CASE REPORTS ----- SODIUM ASCORBATE

NAME	Age	Sex	Diagnosis	History & Findings	Treatment & Results
1.G.H.	8	F	Asthma Food Allergy	At the age of 5, the patient had severe recurrent measles, the attacks which recurred in a series of attacks every 5 to 6 months. The attacks were difficult to control and the patient was sent to Arizona where she remained for 2 years. While in Arizona her attacks were recurrent, but milder. The patient was brought to New York for further study. Nasal examination revealed bilateral ethmoiditis, associated with post nasal discharge and engorgement of the nasal mucosa. The blood picture showed: hemoglobin, 62%, color index, .6 with a slight leukocytosis and moderate eosinophilia.	The patient was placed on Sodascorbate therapy, 3 tablets 3 times a day. The patient was having asthmatic attacks at the time of examination. During the first week of therapy the attacks became much milder and ceased after the second week of therapy. She was on continuous Sodascorbate therapy 3 tablets 3 times daily for over a year with no recurrence of asthmatic attacks. The child gained in weight. The anemia was treated with twice weekly injections of Ironyl for the improvement of the blood picture. Tonsillectomy was also performed. Patient's mother's comment: "The child can now eat most anything without having an asthmatic attack."
2.L.G.	45	M	Nasal allergy, unknown origin, probably Spring trees	For 20 years has had attacks of sneezing from March 20 to May 14. Had many series of allergic testing with no specificity found on scratch tests. During his attacks he had itching of the eyes and nose and typical rhinorrhea associated with nasal obstruction. Tests for the Spring trees were also negative. Despite the negative tests the patient had received several series of desensitization injections with Spring grasses as well as the Spring tree pollens, with no benefit. Nasal examination showed a hyperplastic bilateral ethmoiditis with deflected septum; tonsils had been removed; a septum operation had been performed in February of 1945.	In 1945 he was put on high dosage Vitamin C, 1500 mg. daily with good control of his attacks. The patient stated that he was satisfied with the results. In 1946 the patient came to the office on March 13. He was put on Sodascorbate tablets, 3, 100 mg., 3 times a day. On March 18 he returned to the office and examination showed rhinorrhea, but no sneezing. The dosage was increased to 4 tablets 3 times a day. Nasal examination May 1st, showed no congestion, no rhinorrhea or sneezing. The patient stated that he was having a very good season, even better than the one previously. He had no irritation of the stomach or the bladder, although he had complained of gastric irritation and frequency during the preceding year with the plain ascorbic acid. Patient's comment: "I was never able to sleep from March 21 until May 21, until I started taking the high Vitamin C dosage and later the Sodascorbate tablets."
3.S.R.	35	F	Hay Fever	For last 4 years has had sneezing and running of nose. Hay fever for 17 years. Asthmatic attacks occasionally in hay fever season. Nasal plastic 6 years ago. Findings: Nasal mucosa: Hyperplastic and engorged. Turbinates: Inferior turbinates hypertrophied. Discharge: serous discharge; redness and excoriation of both nasal alae. Allergy testing 4+ to dust and feathers and ragweed. Hapamine series given with no benefit.	Started taking 9 Sodascorbate tablets daily June 15, 1946. During the month of August, until Sept. 10 patient was taking 15 tablets per day. During this time the patient stated that she had no sneezing but a feeling of stuffiness of the nose. This is the first season that the patient has not taken hay fever injections. Patient's Comment: "I had about 10 bad days but these were completely relieved by Sodascorbate."
4.F.S.	28	F	Hay Fever	Has had hay fever for last 8 years. About two weeks ago had nasal obstruction with stuffiness, sneezing and running. Has had hay fever injection series each season up to the present. Examination: Septum: deflected sharply to the left. Turbinates: Inferior turbinates hypertrophied. Mucosa: Hyperplastic, nasal fossae markedly obstructed. Discharge: Mucoid discharge both middle meati, seromucoid discharge. Transillumination: Moderately diminished both sides. Tonsils: removed.	Patient started taking Vitamin C — 100 mg. tablets 2 t. i. d. August 1st, but complained of nausea and gastric disturbance from the tablets. Discontinued taking tablets after 1 week's time and returned to the office 4 weeks later with severe nasal congestion, inferior turbinates congested. Given Sodascorbate tablets 5 t.i.d. Patient then returned 1 week later. During this time the nasal congestion was greatly improved, sneezing very little and patient states that this time is usually the worse part of her season. No gastric disturbance, noticeable from the large doses of Sodascorbate in comparison to the smaller dosage of Vitamin C.

Case Reports

NAME	Age	Sex	Diagnosis	History & Findings	Treatment & Results
5.W.L.	46	M	Hay Fever	Hay fever for 30 years, sometimes accompanied by asthmatic attacks. Findings: Nasal mucosa: Hyperplastic. Septum: markedly deflected to right. Inf. Turbinates: Hypertrophic, profuse sero-mucoid discharge. Bilateral hyperplastic maxillary and ethmoidal sinusitis.	Started Sodascorbate tablets July 15, 1 t.i.d. Patient increased dosage and at the time of the seasonal attack when he would be suffering most, was taking 4 t.i.d. Did not notice any irritation of stomach or bladder. This is the first season that this patient has not had hay fever injections and stated that this is the best season he has had. Very little sneezing. In previous years he would be sneezing continually. Patient regulated the dosage himself in accordance with his needs. Patient's Comment: "I found Sodascorbate very, very helpful to my hay fever condition. As a matter of fact that is now the 4th of Sept. and so far I have suffered practically not at all."
6.G.R.	34	M	Asthma Nasal allergy Generally allergic to all intradermal tests	Asthma in childhood, since age of 5. Has coughing spells, some hay fever attacks; is allergic to molds, pollens, etc. Has had some relief with ascorbic acid. Findings: Nasal mucosa: Hyperplastic. Nasal discharge: Mucoid discharge both middle meati. Septum: moderately deflected to right	Patient started Sodascorbate tablets in January, taking 3 t.i.d. Since the patient is living out of the state, he reports to us via mail. And as he knows his condition, he is able to judge the number of tablets that gives him the most benefit. He states that taking 1000-1200 mgs. a day he reacts more favorably. With the taking of this amount, he is more efficient, calm and less fatigued than otherwise, and with the taking of the larger doses he has had none of the customary allergic reactions (swollen eyes, headache, etc.) as he had suffered previously. Patient's Comment: "I am very grateful to you for the first intelligent approach to a problem which was becoming a very difficult one to me indeed."
7.G.P.	38	F	Hay Fever	Nasal obstruction and discharge, with sneezing and running since November. Has had vaccine injections. Tickling in throat, wheezing in chest. No family history of hay fever or asthma. Findings: Nasal mucosa: Hyperplastic, engorged, allergic in type. Septum: Mid position. Turbinates: polypoid changes Allergic Testing: 4+ ragweed; 3+ timothy.	Sodascorbate tablets started at first visit, 3 t.i.d. Patient left the city but reported via mail that she was continuing with the Sodascorbate tablets and had increased to 4 t.i.d. with very little sneezing, or rhinorrhea. Patient's Comment: "My sneezing seizures seem to be few and far apart."
8.S.D.	48	M	Hay Fever	For last 4 weeks in Sept. has had nasal stuffiness and sneezing moderately. History of hay fever and asthma. Findings: Nasal mucosa: Congested. Septum: Deflected to right and left. Turbinates: Inferior turbinates hypertrophied. Allergy Testing: Ragweed 4+; timothy 4+. Has had hay fever injections with very little relief at this time of year.	The first of July the patient started Sodascorbate tablets, 3 t.i.d. and continued 4-5 weeks then gradually tapered off, taking 2 t.i.d. then 1 t.i.d. Was well through this period. Then for several days went without Sodascorbate and the nose became congested, breathing difficult and sneezing. The patient then started taking 3 t.i.d. again and all symptoms gradually cleared. No irritation of stomach or bladder noticeable. Patient's Comment: "Of all the remedies that have been given me in the past for my allergic condition, I must say that Sodascorbate definitely has proven the most effective."

CONCLUSION

1. The availability of the sodium salt of ascorbic acid for oral use represents a marked advance in the therapeutic approach to allergy.
2. The increased sensitivity to histamine in supra-

renalectomized animals suggests a relationship between adrenal cortical hormone-Sodium-Vitamin C and allergy.

3. In refractory cases of allergy and asthma sodium ascorbate was more effective than ascorbic acid.

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A Study of a Group of Poorly Regulated Diabetic Patients

by

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AUGUSTA, GEORGIA

CONSIDERABLE INTELLIGENCE and co-operation on the part of the diabetic patient is necessary for satisfactory control. These faculties were generally absent in the subjects of the present report; as a result an opportunity was provided for the study of relationships between various degrees of hyperglycemia, ketosis and abnormal body weight.

METHODS AND MATERIAL

The subjects were members of the diabetic clinic in the out-patient department of the University Hospital. Almost every patient who attended the clinic during the period of the study was examined — there was no selection of subjects. The group included 16 white patients, 3 male and 13 female, and 34 negroes, 11 male and 23 female.

Calculated diets were not employed in this study. Experience had shown diet lists to be of no practical value. However, the subjects were advised repeatedly to avoid concentrated fat and carbohydrate foodstuffs, and to subsist largely on a diet of lean meat and green vegetables; and attention was re-

peatedly directed to their condition in relation to ideal weight.

These patients took their insulin (protamine-zinc-insulin) in a single dose daily before breakfast; this plan was adopted primarily because of the factor of simplicity.

Blood for analysis was collected in the diabetic clinic at about three hours after breakfast and the daily injection of insulin. It was assumed that a single specimen collected at this time would have more significance, at least for the level of glucose, than a fasting specimen; this assumption is supported by the observations of Sindoni (1).

The methods employed for chemical analysis were: for blood sugar the Nelson-Somogyi (2) colorimetric procedure, and for acetone bodies the method of Greenberg and Lester (3).

DISCUSSION OF RESULTS

All of the results are assembled in Figure 1. It will be observed that about three-fifths of the patients had a level of blood sugar above 200 mg.% and about one-fourth above 300 mg.%. This poor state of control was accounted for quite frequently by

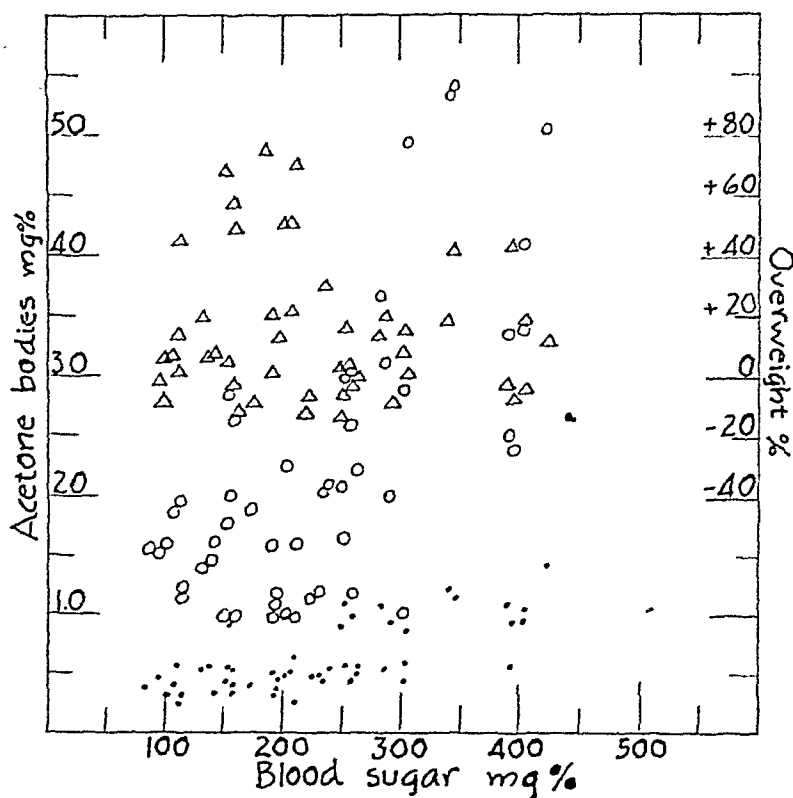


Figure 1. — Chart showing interrelations of hyperglycemia, ketosis and obesity. Dots, free acetone; circles, total acetone bodies; triangles, overweight %.

an admission on the part of the patients that they ran out of insulin, or that they reduced the dose so the supply would last until it was convenient to come to the clinic; and they have usually been little impressed by lectures concerning the danger of such practices.

The ketosis: With the technique employed in this study normal bloods usually gave values less than 0.2 mg.% for acetone, and values less than 1.0 mg.% for total acetone bodies, expressed as acetone. It will be observed then, by reference to the chart, that there is a detectable ketosis in the better regulated members and that the intensity of the ketosis rises rapidly with poorer control, and also that the free acetone represents a substantial fraction of the total acetone bodies.

Ordinarily the finding of a ketosis is taken as evidence of very poor control; patients who have intermittent glycosuria but "no ketosis" are said to be in fair control. It should be noted that such expressions are usually based on the examination of the urine with nitroprusside; only the poorest regulated members of this group gave a positive nitroprusside reaction. Presumably the cause of a negative nitroprusside reaction on the urine in the presence of a mild ketosis is the activity of the renal tubules in reabsorption of acetoacetic acid; acetone is always present in the urine at the same concentration as in blood (4), but gives less color with nitroprusside than acetoacetic acid. It is only when the intensity of fat metabolism in the uncontrolled diabetic patient reaches a high level, about 2.5 gm. fat/kg./day

(5), that acetoacetic acid is excreted to a significant degree in the urine.

The observed relation of the ketonemia to the lack of control brings up the question of the management of diabetes based on tests which indicate the level of this ketonemia. That glycosuria provides an imperfect basis for control is generally recognized; John (6) has recently called attention to the unpredictable level of the renal threshold for glucose, and also to other objections — his recommendation is for the daily determination of blood sugar.

Probably few patients will ever submit to daily blood chemistry. However, an index to the level of the ketonemia may be obtained by a determination of the acetone in expired air, and a clinical test for this purpose has been described (7). Unfortunately the test requires a great deal of intelligent cooperation on the part of the patient and also some training on the part of the observer; my own experience with the method has been somewhat disappointing. Nevertheless it would appear that the best hope for a better basis of control waits on the development of a good clinical method for acetone in urine or alveolar air.

The energy balance: A glance at the chart reveals that there is no correlation between excess weight and hyperglycemia. This should suggest that unrestricted diet was not an important cause of the poor state of control. It is true that 44% of these patients were more than 10% above normal weight, which compares unfavorably with the well regulated

group reported by Richardson and Bowie (8) in which only 18% were this much overweight. However, most of the very obese had blood sugar in the vicinity of 200, and only a minimal ketosis; some of the poorest regulated had approximately normal weight. Obviously in about one-half of the group the sense of appetite functioned in a fairly normal manner, so that the caloric intake approximately equaled the energy expenditure. Dietary restriction in such patients could have served no useful purpose, providing the intake of protein and other essentials of nutrition was adequate; evidences of nutritional deficiency have been uncommon among these patients.

Most likely the merits of the calculated diet and the evils of the free diet have each been exaggerated. The free diet is usually pictured as one which entails the waste of 10% or more of the carbohydrate of the diet as sugar in the urine. This is not necessary. If the patient will test his urine two or more times daily and adjust the insulin dosage so as to minimize glycosuria, there is no reason for excreting more sugar on a free than on a calculated diet. The chief merit of the calculated diet depends on the extent to which it prevents overeating, since it is no longer felt necessary to carefully balance ketogenic and antiketogenic foods. Often the physician fails to consider the futility of trying to prescribe a diet with a caloric value which will just match the variable energy expenditure of the ambu-

latory patient. What usually occurs is that the patient receives a diet with somewhat less than the actual caloric requirements, and then proceeds to eat just enough extra to balance his activity.

If the patient's sense of appetite fails so that the caloric intake exceeds the energy expenditure, then treatment of the obesity is in order. For the purpose of dietary restriction, a few simple instructions concerned with the elimination of concentrated food-stuffs will usually accomplish as much as a carefully calculated diet.

The conclusion to be drawn is that the better results observed in the group studied by Richardson and Bowie (8) were due to the fact that the inclination and capacity for following instructions was more frequent among their subjects than in the group reported here.

SUMMARY

Observations were made relative to hyperglycemia, ketonemia and obesity on a poorly regulated group of clinic patients. The levels of acetone and total acetone bodies were slightly elevated in the better regulated members, and there was a rough correlation throughout between the ketonemia and hyperglycemia. There was no correlation between excess body weight and the state of control. Certain implications were suggested relative to the importance of a calculated diet in the management of diabetes.

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Book Review

24-Hour Variations of Gastric Function. By Erik Forsgren. Pp. 34. Hakan Ohlssons, Lund, 1946.

By performing four or five Ewald gastric analyses daily on a group of patients suffering from tuberculosis, the author believes that the laborious procedure was valuable in showing that patients with ulcer or achylia tend to present a "rhythm" in their 24-hour secretion, so that an ulcer case will show periods of reduced acid secretion during the daytime and a per-

son labelled "achylia" on the basis of a single analysis may show some slight gastric activity. He feels that maintenance of the "rhythm" peculiar to the individual is important from a nutritional standpoint. He finds that in tuberculosis the rhythm is disturbed and when it can be restored by proper dietary and medicinal help, the healing of the pulmonary lesions is hastened. He makes a plea for a new instrument to measure gastric acidity continually by electrical means.

Abstracts Of Current Literature

CLINICAL MEDICINE

Mouth and Esophagus

MOLLER, K. L.: *Purulent inflammation of the salivary glands in infants.* (Nordisk Med., June 13, 1947, 1360-1362).

Acute purulent salivary gland inflammation in infants constitutes a clinical entity. Staphylococci usually are the causative agents and may reach the glands from the mouth via the salivary ducts. Prognosis is favorable. Penicillin gave good therapeutic results.

COUMOULOS, H. AND MELLANBY, M.: *Dental condition of five-year old children in institutions and private schools compared with L. C. C. schools.* (Brit. Med. J., May 31, 1947, 751-756).

Although there was a direct relation between the structure of the teeth and the incidence and extent of caries among children of each group — that is to say, the better the structure the less the caries — this did not hold between children of the different groups: thus in the institutional group, teeth of a given grade of structural defect had much less caries than teeth of the same structure in either of the other two groups. This probably is to be explained on the basis of the calcifying properties of the respective diets at different periods, both pre-eruptive and post-eruptive. Probably in the London County Council schools, the diets were the worst.

NEUHAUSER, E. B. D. AND BERENBERG, W.: *Cardio-esophageal relaxation as a cause of vomiting in infants.* (Radiology, May 1947, Vol. 48, No. 5, 480-483).

X-ray films are shown indicating various degrees of relaxation of the cardia and of the hiatus esophagus, an occurrence explaining some instances of vomiting in infants. The clinical symptom of importance is persistent regurgitation alleviated by placing the patient in the erect position. By fluoroscopic examination, retrograde filling of the esophagus during inspiration or with increased intra-abdominal pressure is seen in association with persistent relaxation of the hiatus. The condition is usually a temporary aberration of the neuromuscular function of the hiatus portion of the esophagus and diaphragm.

RAU, L.: *Paterson-Plummer-Vinson syndrome in a case of familial acholuric jaundice.* (Proc. Roy. Soc. Med., XL, 6, April 1947, 271-272).

A case is presented which showed a combination of acholuric jaundice and sideropenic dysphagia. Esophageal spasm occurred at a point just above the aortic knuckle, although usually in the Paterson-Plummer-Vinson syndrome it occurs just below the level of the cricoid cartilage. Immediate response to

the administration of Bland's pills was noted. Patients suffering from sideropenic dysphagia are perhaps prone to develop a retrolaryngeal or hypopharyngeal carcinoma and should be followed up for long periods with this complication in mind.

Liver and Gallbladder

LUBBY, D. H., SHANK, R. E., KUNKEL, H. G. AND HOAGLAND, C. L.: *Intravenous therapy of cirrhosis of the liver.* (J. A. M. A., April 19, 1947, 133:16, 1181-1190).

Frequent large intravenous doses of a specially prepared, crude liver extract to patients suffering from hepatic cirrhosis, for periods ranging from six months upwards, and without special dietary precautions, caused return of appetite, increase in caloric intake, gradual disappearance of ascites in the majority of cases, improvement in liver function tests, better tolerance of paracentesis. Five patients treated from ten to 18 months have been placed on treatment-free observation for periods ranging from four to 15 months, without showing clinical or biochemical relapse. Wasting is controlled and protein storage restored.

VALENTINE, E. H.: *Liver Function Tests.* (Pennsylvania Med Journ., 50:6, 602-605).

The author gives a valuable critique of the uses of hepatic function tests. In the evaluation of general liver function, the *bromsulfalein test* (using the larger dose of 5 mg. per kilogram of body weight), is the best, but where jaundice is present, the *hippuric acid test* is preferable. Intrinsic parenchymal disease of the liver is best detected by the *cephalin-cholesterol Flocculation Test*. For the same purpose, the *Thymol Turbidity Test* is technically simpler and somewhat more dependable, but it does not become positive as early in the course of infectious hepatitis as does the cephalin-cholesterol flocculation test. In the *Cholesterol Esters Test*, a rise in the percentage of cholesterol appearing as esters signals improvement and a fall signals retrogression. For identifying the mechanism of jaundice, the *bilirubin and urobilinogen tests* and *prothrombin test* are most valuable.

BOCK, J.: *Cirrhosis of the liver in the aged.* (Nordisk Med., 23, 34, June 6, 1947, 1295-1299).

In Scandanavia in recent years the female sex is predisposed to the malignant form of epidemic hepatitis and hepatic cirrhosis is now found more frequently in females than males, contrary to the findings of a few years ago. This cannot be explained either by the fall in the consumption of alcohol or the presence of German troops in Denmark. Obviously some new factor in the pathogenesis of cirrhosis must be looked for. Occasionally cirrhosis is sub-clinical and the finding only made at post-mortem.

RIGLER, L. G. AND MIXER, H. W.: *Cholangiography and biliary regurgitation*. (Radiology, May, 1947, Vol. 48, No. 5, 463-471).

The authors describe immediate cholangiography (made at operation) and delayed cholangiography (made post-operatively) by injecting a contrast medium into the common duct or gall bladder. It can also be accomplished by using a peritoneoscope to introduce a needle into the gall bladder. Pictures thus obtained are of value to the surgeon, revealing stones, kinks, etc., in the ducts and hepatic radicles. The preferred medium is diotrast. Out of a total of 126 patients so examined, there were 8 with obstruction of the common duct whose films revealed filling of the renal pelves also. This is explained by a "regurgitation" of the diotrast into the blood stream, via the hepatic lymph spaces and sinusoids, due to increasing the pressure of injection above the excretory pressure of the liver (350 mm. of water). At times reactions follow, due probably to forcing bacteria through the liver.

SURGERY

SPALDING, J. M. K.: *A case of phaeochromocytoma*. (Brit. Med. J., April 26, 1947, 564-565).

The author describes the successful surgical extirpation, followed by cure, of a chromaffin tumor of the right adrenal gland in a young woman of 24 who for two years had experienced almost daily attacks of paroxysmal hypertension. The blood pressure rose to 300/200 during an attack. Her usual blood pressure ranged from 120/80 to 250/170 between the attacks. She complained of blurring of vision and of attacks of upper abdominal pain and vomiting with palpitation and headaches. Retinal hemorrhages were present. A tumor weighing 86 grams was removed from the right flank and proved to be a phaeochromocytoma. Recovery was uneventful and 15 months after operation the patient was doing a full time clerical job, the blood pressure being 135/100.

WYATT, O. S. AND CHISHOLM, T. C.: *Acute intussusception in infancy and early childhood (a review of fifty-five consecutive cases)*. (Journal-Lancet, May, 1947, LXVII, 5, 193-195).

Acute intussusception, which constitutes an emergency in infancy and early childhood, can usually be diagnosed on the basis of a classical history of intermittent severe seizures of abdominal pain, of a palpable sausage-shaped mass in the abdomen and of bright red blood in the feces. The barium enema is frequently a helpful diagnostic weapon, but when employed therapeutically, its dangerous shortcomings must be carefully recognized to avoid unwarranted medical tragedies. Surgical intervention with special pre-operative precautions constitutes the treatment of choice. Only thus can the existing mortality be reduced.

BAILEY, H.: *Parotidectomy: indications and results*. (Brit. Med. J., March 29, 1947, 404-407).

The surgeon describes an operation by which cure may be obtained without facial nerve injury or salivary fistula, based on a new conception of the anatomy of the parotid. Radiation therapy is useless because the gland is radio-resistant. In the past many surgeons have side-stepped the operation because of its technical difficulties and popular ideas as to its danger.

HINE, W. N.: *A case of mesenteric thrombosis complicating multiple wounds*. (Brit. Med. J., March 29, 1947, 380-381).

A case of mesenteric thrombosis following leg wounds is described in which 91 inches of gut was removed, with complete recovery.

MARTINSON, L. F., GILLESPIE, S. R., DUNCAN, D. G., AND SEVEREIDE, A. L.: *Carcinoma of the head of the pancreas*. (Northwest Med., April 1947, 46:4, 283-285).

A case is described in detail in which a successful operation was done for cancer of the head of the pancreas by the Whipple operation. The diagnosis was made at operation, but the case was thought at first to be one of peptic ulcer because of serious hemorrhage with hematemesis and tarry stools. The authors point out that the presence of blood in the stools should cause the physician to look for cancer of the head of the pancreas in cases in which the source of the bleeding is not obvious, and this applies particularly in case of obstructive jaundice with melena.

CLAGETT, O. T.: *Surgery of the pancreas*. (Texas Med. J., May 1947, XLIII, 1, 12-16).

The author reports extensive pancreatic resections at the Mayo Clinic for carcinoma, chronic pancreatitis, pancreatic lithiasis and hyperinsulinism due to benign adenomata. In cancer and in chronic pancreatitis, pain referred to the back is a leading symptom. A good deal of the paper is devoted to arguments for and against the anastomosis of the cut end of the pancreas to the intestine. The procedure avoids pancreatic fistula and it may improve digestion, but it adds considerably to the gravity of an already ponderous and dangerous operation.

GUTMANN, D.: *Medullary suprarenal chromaffinoma producing malignant hypertension*. (Brit. Med. J., April 26, 1947, 563-564).

The case of a woman of 38 is described who suffered attacks of paroxysmal hypertension, the blood pressure rising, in the attacks, to 300/176, then falling, after the attacks, for a time, to 100/60, gradually regaining its usual chronic level of 200/120. Attacks were precipitated by turning on the right side and were characterized by tachycardia (130).

tachypnoea and drenching sweats. The tumor was located by the X-ray appearance of a pressure on the hylus of the right kidney. Death in an attack prevented operation. Necropsy showed a medullary suprarenal chromaffinoma one inch in diameter. The kidneys gave the appearance of a nephritis associated with malignant hypertension, thinning of the cortex with dispersed necrotic areas. Uremia preceded death.

METABOLISM AND NUTRITION

ANDERSON, J. A.: *The quantitative aspects of fluid therapy in infants and children.* (Journal-Lancet, May 1947, LXVII, 5, 185-189).

The importance of dehydration in infants and children is stressed and quick methods of calculating the amount of fluid necessary for rehydration are given. Dehydration is always more serious in children than in adults. Irreversible changes in the brain, liver, kidney and heart may occur during profound dehydration with loss of electrolytes. Hemo-concentration, as indicated by the hemoglobin, the hematocrit and the plasma protein concentration are increased to high value in severe dehydration.

NASIO, J.: *Effect of ascorbic acid upon cincophen experimental peptic ulcers.* (Rev. Gastroenterology, May 1947, 14, 5, 340-344).

The author found that the simultaneous administration of cincophen and 500 mg. of ascorbic acid per day to dogs during periods of time ranging from 13 to 22 days prevented the appearance of peptic ulcers in over 60 per cent of the cases. This work suggests the use of ascorbic acid as a complementary agent in the treatment of human gastroduodenal ulcer.

HALL, G. B.: *Nutritional deficiency diseases.* (Med. Jour. Australia, April 5, 1947, 14, 430-434).

The influence of deficiency disorders on the nervous system is discussed, with the statement that nutritional deficiency embraces deficiency of caloric requirements, deficiency of variety foods, especially protein and carbohydrate, fluid deficiency, vitamin deficiency, mineral deficiency, oxygen deficiency, and infinite admixture of these. The article limits itself to vitamin deficiencies and protein deficiency. He stresses the fact that the use of paraffin and similar aperients interfere with absorption of vitamin A and carotene. Ocular effects of vitamin A deprivation include xerophthalmia, Bitot's spots, asthenopia and night blindness. Lack of vitamin A probably plays a part in lathyrism and perhaps in toxigenic convulsive ergotism. The good effect of vitamin A in respiratory infections is due to its improvement of epithelium but it does not possess a direct anti-infectious power. Lack of vitamin D causes a fall in the blood levels of phosphorus or calcium, or both, bringing about increased irritability at neuro-muscular junctions, resulting in tetany, spasmophilia, and retardation in ossification in growing bones. He believes that large doses of vitamin D may cause serious and wide-

spread deposition of calcium in many vital tissues.

Thiamin combines with pyrophosphoric acid to form pyrophosphate, a cocarboxylase which acts on pyruvic acid, an intermediate product in the breakdown of glucose. Deprivation of thiamin halts the breakdown at this stage and pyruvates accumulate above the normal blood level of 4.7 mgm. per centum. Neurological lesions resulting from vitamin B₁ deficiency are due to the inability of the nervous tissue to metabolize glucose efficiently. Heart muscle "hangs on to" thiamin longer than any other tissue, due to a great storage capacity. Nerve tissue has no capacity for storage of thiamin. The B vitamins are intimately concerned with, and produce their effects, as results of disturbances* of tissue respiration. *Riboflavine* is an essential constituent of the flavo-protein enzyme system which takes care of the avascular cornea, in which tissue no hemin substances are present. Deprivation of riboflavine results in vascularization of the cornea — nature's attempt to overcome a local asphyxia. *Nicotinic acid* is necessary in the cure of pellagra but the cheilosis, perleche and seborrheic dermatitis of the naso-labial folds are caused by lack of riboflavine, and the neuropathy present depends on lack of thiamine. He refers to Jolliffe's *nicotinic acid deficiency encephalopathy*, usually fatal, but sometimes cured by nicotinic acid.

FOSS, H. L. AND KLINGER, H. M.: *Hyperthyroidism without goiter.* (Pennsylvania Med. J., 50:6, 591-597).

The chief importance of this paper lies in the fact that the authors are able to make out a good case for the existence of hyperthyroidism in many patients who have no visible, or actual, enlargement of the thyroid gland. Most, if not all the cases, conform to the diagnosis of "Grave's Disease" with exophthalmos, weight loss, tachycardia and elevation of the basal metabolism. Since they weighed the tissues removed in each case, they make the point that the gland was not enlarged. B.M.R.'s were done under truly basal conditions and so they may be regarded as reliable. Above all, they were improved or cured by removing 90 per cent of the gland. They have found the toxicity of thyroids to be in inverse proportion to their size. They have found that propylthiouracil is excellent for pre-operative treatment and does not exert the toxic effects sometimes associated with thiouracil. All physicians should be on the lookout for cases such as these, most of which are treated as heart cases.

BOLLINGER, A.: *Recent observations on uric acid.* (Med. Journ. Australia, Mar. 29, 1947, 1:13, 394-395).

The author has found large amounts of uric acid in the hair of certain animals, the fur of rabbits and in the feathers of some birds. It is possible that the appearance of uric acid in high concentration in these integumental appendages may indicate that, in these species, we have discovered a mode for the excretion of uric acid. Human hair also contains large amounts of uric acid, but, thus far, too few cases

of hair from gouty patients have been examined to lead to any conclusions.

NORTHROP, MARY W. AND PIPER, GERALDINE M.: *A study of diets of patients in a prenatal clinic with an attempt to correlate dietary adequacy with physical findings.* (Northwest Medicine, April 1947, 46, 4, 294-298).

By studying the usual pre-partum diets of 42 pregnant women, the authors were able to place 22 in a group in which the diet was *good or fairly good* and 20 in a group in which the diet was *poor*. Questionnaires and diet memos were employed to gain the dietary information. Infant death was three times as great in the poor diet group and toxic symptoms in the mothers were about twice as great. Lactation was much more successful in the well-fed group of mothers. In studies by Burke, to which reference is made, every infant death within a few days of birth and all premature infants were born to mothers whose diets were very inadequate in *protein*.

PARR, L. J. A. AND SHIPTON, E. A.: *The beneficial effects of yeast in diabetes mellitus.* (Med. Jour. Australia, Mar. 22, 1947, 12, 365-367).

The administration of baker's yeast (in a hydrolyzed form known as "Amino-B") in daily amounts equivalent to about 1 to 2 ounces of baker's yeast caused a fairly definite, sometimes marked reduction in insulin requirements and in the blood sugar levels and the urinary glucose, as well as curing associated neuritis and fatigue. The authors suspect that some element in the product, some of the available amino-acids, have a favorable effect on the cells of the pancreas or liver, or both. The treatment was least effective on old patients with long standing disease. Thiamin is not the element of yeast which caused the improvement in the insulin requirements.

NORRIS, THELMA J.: *Nutritional survey of Tasmania: 1. Food consumption and dietary levels of the spring of 1945.* (Med. Jour. Australia, March 29, 1947, 1, 13, 399-403).

In 1945 a careful enquiry, involving food consumption survey, medical examination of children in metropolitan households with particular reference to signs and symptoms of deficiency disease, and finally the determination of the plasma ascorbic acid levels of these children, showed that with few exceptions the food consumption and dietary levels in Tasmania showed a higher potato-cereal and a lower protective food consumption than on the mainland of Australia. The findings closely paralleled others made in 1944. The intake levels of calcium and vitamin C probably are insufficient to ensure optimal health. Many households were too low in calories and in specific nutrients. The survey demonstrated that the results obtained by the method of sampling and data collection, used in the 1944 survey, are reproducible and give a true picture of the mean food consumption and dietary pattern of the population under consideration.

HARRIS, A. D. AND MOORE, T.: *Vitamin A in infective hepatitis.* (Brit. Med. J., April 29, 1947, 553-559).

The plasma levels of vitamin A and carotenoids were observed in 32 cases of infective hepatitis, none of whom had had blood transfusions. These levels were found to be low, often very low, in the early stages of the disease, of the grade of 30 i. u. per 100 cc. as compared with an average of 118 i. u. previously found for normal subjects, and this low plasma vitamin A seems an adequate cause of the impairment of dark-adaptation in this disease. The degree of pyrexia and the age of the patient appeared to influence the extent of the fall in plasma vitamin A, both in direct proportion. The vitamin A reserves of the liver were not seriously reduced and the plasma vitamin A increased during convalescence until the mean for all cases equalled or exceeded the mean for normal subjects. The changes in plasma vitamin A and carotenoids went roughly parallel with the prothrombin value and with hippuric acid tolerance, and moved in an opposite direction to the plasma bilirubin. It appears that in infective hepatitis, the mechanisms responsible for the absorption of vitamin A from the intestines, for its deposition in the liver, and for its release into the blood stream are not always affected to the same degree.

MISCELLANEOUS

SOEBORG-OHLSSEN, A.: *Contribution to the histochemistry of the stomach.* Thesis; H. Hagerup, Copenhagen, 1941.)

The investigation deals with the occurrence and distribution of the proteolytic enzymes in the fundic and pyloric mucosa in pig and man. The enzymes considered are pepsin, cathepsin, carboxypolypeptidase, aminopolypeptidase, dipeptidase, prolinpeptidase and urease. The technique employed is that developed by K. Linderstrom-Lang and H. Holter. A description is given of this technique and of the substrates and extraction agents used. The experimental results show the distribution of dipeptidase and aminopolypeptidase in the pyloric mucosa. The occurrence of these enzymes is here found to be independent of each other. The dipeptidase is predominant in the regions of the pit epithelium and the neck chief cells, while the two enzymes are equally distributed in the chief cell region. In the fundus the aminopolypeptidase shows considerable predominance in the regions of the parietal cells, the neck chief cells and the chief cells, while the dipeptidase, as in the pylorus is predominant in the region of the pit epithelium. The pepsin activity is very small in the pylorus, while in the fundus it is very considerable in the layers of the chief cells. Thus there is a difference in the distribution of pepsin and aminopolypeptidase. The cathepsin action in the pylorus must undoubtedly be ascribed to pepsin since activation with HCN fails. Dipeptidase and aminopolypeptidase characterize the pyloric mucosa while pepsin is the characteristic feature of fundic mucosa. Prolinpeptidase is evenly distributed over all cell types in

pylorus and fundus. The presence of carboxypolypeptidase can not be demonstrated. The presence of urease in the pyloric and fundic mucosa of pigs is dubious. In case of man, urease activity is found in the regions of the pit epithelium and the neck chief cells. The manner of distribution of dipeptidase and aminopolypeptidase in the pyloric mucosa is the same in man as in pig. Pepsin has a distribution in human fundus and pylorus corresponding to the distribution in the same regions of the stomach of the pig. — Courtesy Biological Abstracts.

KAYWIN, L.: *Emotional factors in urticaria*. (Psychosomatic Medicine, March-April, 1947, IX, 2, 131-136).

For some time, emotional factors have been known to play a role in urticaria (possibly in 15 per cent of cases) and the author describes in psychological detail three persons suffering from this skin affliction in whom emotions played a prominent part. Such an emotional relationship may be recognized through a history of an unhappy and rather anxiety-provoking existence for a period preceding the onset of symptoms, with a sudden onset of symptoms, precipitated by a frustrating experience. The personality tends to be shy, easily embarrassed, prone to blushing, relatively passive-dependent and immature and with a tendency toward exhibitionism.

MACNEAL, P. S. AND DAVIS, D.: *The use of methyl-iso-octenylamine in migraine*. (Annals Int. Med., April 1947, 26, 4, 526-527).

"Octin" avoids some of the unpleasant side-effects attending the use of ergotamine tartrate, but has certain other disadvantages of its own. It tends to elevate the blood pressure promptly and should be avoided in cases of hypertension. Apart from this precaution, it may be tried out on migraine cases and used in those in whom it gives prompt relief of the individual attacks. Trial doses of 50 to 75 mgm. are used, but the effective dose is usually between 100 and 200 mgm. Obviously "octin" is not suitable for treating all patients with migraine, but it is superior to ergotamine in those who tolerate it, for it produces no nausea nor does it cause peripheral vasoconstriction in the hands, as ergot sometimes does.

OAKLEY, C. L.: *The constituents of normal human blood*. (Proc. Roy. Soc. Med., Mar. 1947, XV, 5, 190).

Counts of red or white blood cells in animals show a variation seldom less than 10 per cent and usually more, whereas in man very little variation occurs. This may be due to man's large size, low metabolic rate, and consequent long cell survival time. Women have less hemoglobin than men. Americans have higher hemoglobin concentrations than Britons, a fact which Price-Jones attempted to explain by supposing that Americans, who spend a high proportion of their time in automobiles, suffer from a mild chronic monoxide poisoning, with resulting plethora.

SCHROEDER, A. J.: *Nutritional and psychological aspects of the cure of patients with bulbar poliomyelitis*. (Journal-Lancet, LXVII, 5, 199-201).

In patients with bulbar poliomyelitis who developed dysphagia or complete inability to swallow, it was found that gavage tubes (No. 12 to No. 16 French tubes) could be easily passed into the stomach, because of the existence of soft palate and pharyngeal paralysis and depressed gag reflex. It was found by feeding through the tube that much time could be saved by reducing the usual parenteral procedures. The method proved quite safe. Specimen feedings were given. Psychological difficulties of the patients were reduced by discussion of their uncertainties and apprehensions.

WHEATLEY, D. P.: *Massive penicillin doses in general practice*. (Brit. Med. J., April 19, 1947, 530-531).

The author records cases of boils, carbuncles, whitlows, conjunctivitis and styes in which doses of 200,000 units of penicillin daily effected perfect and rapid cures without local treatment of any type.

TILLGREN, N.: *Huvudvarksundersokningar med dihydroergotamintartrat*. (Nordisk Medicin, 16, 34, April 18, 1947, 937-941).

Treatment of headache with dihydroergotamine tartrate: Dihydroergotamine tartrate relieved migraine almost as effectively as did ergotamine tartrate, but the effective dosage was found to be about twice that of the latter. It had a favorable effect in certain cases of headache due to hypertension. Intravenous injection, in proper doses, caused the same ill effects as ergotamine tartrate (nausea, vomiting) though probably less marked. Intravenous injection raised the systolic and diastolic blood pressure, though seldom markedly, the rise being about the same as followed the injection of half the amount of ergotamine tartrate. Angina pectoris was provoked in one patient with coronary disease and labor was induced in one pregnant woman. The contraindications are about the same as for ergotamine tartrate.

DAVIDSON, L. S. P. AND GIRDWOOD, R. H.: *Folic acid as a therapeutic agent*. (Brit. Med. J., May 3, 1947, 587-591).

The authors obtained satisfactory hematological responses in 16 cases of pernicious anemia in relapse by the oral administration of folic acid in doses varying from 2.5 mg. to 20 mg. daily. They believe that in all cases that folic acid in a dosage of 5 mg. daily will restore the blood quantitatively and qualitatively to normal in Addisonian anemia. Large massive single doses of from 200 mg. intramuscularly to 400 mgm. orally, gave excellent hematopoietic responses which, however, lasted only for two weeks. One case of undoubted Addisonian anemia which did not improve on folic acid did show a perfect response to liver extract. This case developed an infectious peripheral neuritis which produced severe

agranulocytosis and may have interfered with the action of folic acid. In three cases of subacute combined degeneration of the spinal cord treated with folic acid, no improvement occurred in any and in one case the neurological features rapidly deteriorated, whereas in all three cases marked improvement occurred after substitution of liver extract therapy. The authors encountered a refractory case of megaloblastic anemia (not Addisonian) in whom the hemoglobin and red cell count became normal on folic acid but a megaloblastic smear picture persisted, but whose blood picture became normoblastic on the use of proteolyzed liver. One case of pernicious anemia continued to show a megaloblastic picture and refractoriness to liver extract, but became normoblastic on the use of folic acid. Aplastic and hypoplastic anemia, leucopenia and thrombocytopenia did not show any response to folic acid therapy. In tropical sprue and idiopathic steatorrhea, dramatic control of the diarrhea and rapid clinical improvement occurred following folic acid treatment. Ulcerative colitis was not benefitted. It appears that a hematological response to folic acid occurs only in patients suffering from a megaloblastic form of anemia. Free folic acid seems to be the factor essential for continuation of normoblastic blood formation and a deficiency causes a reversion to the megaloblastic state. It can be assumed that purified liver extracts contain a *liberating factor* which enables the conversion of conjugated folic acid to free folic acid to take place. The cause of pernicious anemia does not lie in some inherent abnormality of the bone marrow but in the inability of the body to convert conjugated folic acid to free folic acid. The liberating factor (L. F.) is the result of the interaction of Castle's intrinsic and extrinsic factors and is absorbed from the intestine and stored in the liver.

FORBES, GILBERT: *Poisoning with a preparation of iron, copper and manganese.* (Brit. Med. J., Mar. 1947, 367-370).

Two boys died after ingesting tablets containing Ferrous sulfate exsic. 3 gr., copper sulphate 1/25 gr. and manganese sulfate 1/25 gr. One boy swallowed 50 and the other 30. Autopsies showed extensive liver damage and, from animal experiments, it was concluded that the hepatic disease was due to the ferrous salt. Ferrous sulfate on contact with gastric juice is converted to the chloride which has an irritant action.

SELLERS, E. A. AND BEST, C. H.: *Effects of certain diets on the loss of nitrogen in urine after experimental burns.* (Brit. Med. J., April 19, 1947, 522-534).

Experiments were undertaken to find out if certain

diets lessened the urinary loss of nitrogen after experimental burns. A methionine supplement (one per cent) to a stock diet did not reduce the urinary loss after burning, unless a methionine deficiency in the basal diet had existed prior to the burning. Cystine, choline and lysine were ineffective in reducing the urinary nitrogen loss. It is apparently only in young, methionine deficient animals that the addition of methionine reduces the urinary nitrogen loss following burns.

v. SYNOW, G.: *Hypothrombinemia and cerebral injury in a newborn infant after dicoumarin treatment of the mother.* (Nordisk Med., May 16, 1947, 20, 34, 1171-1172).

A woman of 44 during pregnancy contracted a crural thrombosis which was treated with dicoumarin in repeated doses from Sept. 25 to Oct. 24 (a total of 1.75 g of dicoumarin being given). Oct. 26 delivery began. The prothrombin index of her blood was then 33, and it went on decreasing to a minimum value of 16 two days later, after which it was again made normal by a large dose of vitamin K. The delivery lasted three and a quarter hours and occurred in anterior brow presentation. There was remarkably little loss of blood at delivery.

The infant had a birth weight of 2,600 g. By routine, it was given 1 mg. of vitamin K immediately after birth. On examination a few hours later the forehead and skull were covered with extensive subcutaneous hemorrhages. The prothrombin index was less than 10, i.e., extremely low. A new dose of 10 mg. of vitamin K was now given parenterally but without any obvious effect on the prothrombin index. Repeated daily doses of vitamin K both perorally and parenterally did not raise the prothrombin index until six days after birth, after which it increased rapidly to normal values.

At three weeks of age, the infant presented signs of a hydrocephalus, and this then gradually increased in the months following. The hydrocephalus is supposed to be of traumatic origin and, if so, must be connected with the severe hypothrombinemia at birth, which was in its turn caused by the dicoumarin treatment of the mother.

Dicoumarin treatment in pregnancy recently has been argued for on widened indications and has been said not to be especially risky to the pregnant woman. The case related, however, suggests that it may be dangerous to the infant. It should not be given, therefore, in pregnancy unless it is considered strongly indicated with regard to the mother and, then, the resulting hypoprothrombinemia should be suspended at the start of delivery by giving large doses of vitamin K to the mother.

Metabolism of Sucrose: II*

By

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with the technical assistance of

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IN 1945, the writer (1) showed by means of venous blood sugar estimations at one-minute intervals that, notwithstanding the necessary preliminary hydrolysis, sucrose is capable of restoring the blood sugar to the normal level in cases of insulin hypoglycaemia very rapidly. Of the ten experiments reported, an increase of blood sugar was noted within one minute in two cases; within two minutes in two cases; within three minutes in three cases; within four minutes in two cases, and within five minutes in one case. "Emotional" hyperglycaemia from the frequent needle punctures was excluded. In Chart I are graphically recorded (a) the average blood sugar time curve of these ten cases and (b) the average of three curves, indicating absence of "emotional" hyperglycaemia. The subjects who did not recover within five minutes were of no particular interest in this study and, therefore, were not reported.

VENOUS vs. ARTERIAL BLOOD SUGARS

The use of venous blood in these experiments was based upon the different effects of ingestion of sugar upon arterial and venous blood, depending upon the

sugar contents of the latter in the basal state. Normally, following ingestion of dextrose, the sugar content of the arterial blood increases more rapidly than that of the venous blood and, also, reaches a higher level (2, 3). This is shown in Chart 2.

FIGURE II

ARTERIAL AND VENOUS BLOOD SUGAR TIME CURVES FOLLOWING INGESTION OF DEXTROSE

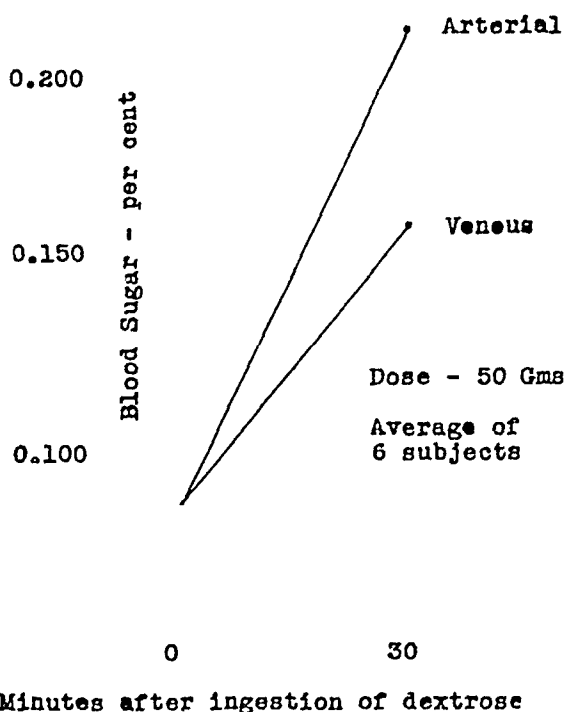
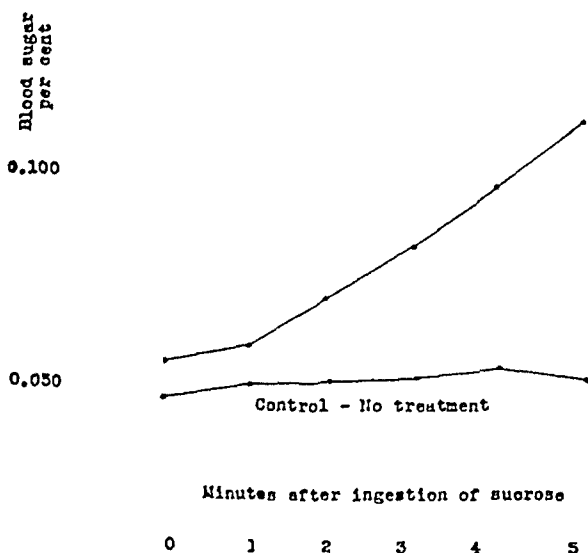


FIGURE I

SHORT PERIOD BLOOD SUGAR TIME CURVES FOLLOWING INGESTION OF SUCROSE IN CASES OF INSULIN HYPOGLYCAEMIA

(Average of 10 cases)



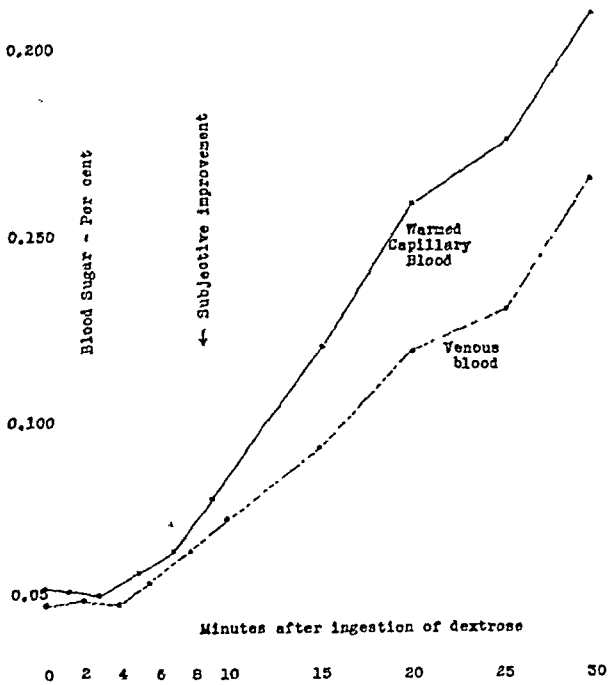
It will be noted that the increase of sugar in the venous blood during the first few minutes after ingestion of the dextrose was almost within the limits of the experimental error of the test. Determination of the sugar content of arterial blood at one-minute intervals is, however, not only very difficult but also hazardous because of the necessary arterial punctures. Capillary blood may be made to approximate arterial blood by warming the skin at the site of the needle puncture, but the sources of error are many, both in the collection of the sample of blood and in the chemical analysis, in common with all micro methods. Advantage was, therefore, taken of the observation that, when the sugar content of the blood is artificially reduced below the normal level, as by injection of insulin, the first response to ingestion of sugar is not, as a rule, oxidation or storage of sugar in the tissues, but restoration of the sugar content of the blood to the nor-

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mal level. This is shown in Chart 3, in which are graphically recorded arterial and venous blood sugars in a case of insulin hypoglycaemia, before and after administration of dextrose. It will be noted that, until the sugar content of the blood was restored to the nearly normal level, the concentration of sugar in the venous blood increased at approximately the same rate as in the arterial blood. Therefore, until the sugar content of the blood has been restored to the normal or nearly normal level, venous blood is as satisfactory as arterial blood. It also has the advantage that it may be readily obtained without any hazard at one-minute intervals.

FIGURE III

ARTERIAL AND VENOUS BLOOD SUGAR TIME CURVES FOLLOWING
INGESTION OF DEXTROSE IN A CASE OF INSULIN HYPOLYCAEMIA



PRELIMINARY COMPARATIVE STUDIES
WITH DEXTROSE AND LAEVULOSE

In all of the above experiments with sucrose, the conditions were such that delayed emptying time of the stomach was excluded as much as possible (tonicity of the sugar solution, etc.) (1). That rapid entry of the sucrose into the intestines was, however, not alone the explanation of the rapid increase of sugar in the blood was suggested from the few comparative studies (unpublished) under the same conditions with dextrose, laevulose and a mixture of dextrose and laevulose which corresponded to the amount of sucrose employed. From these few experiments, it appeared that sucrose was capable of restoring the blood sugar to the normal level more rapidly than dextrose. That the more rapid action of the sucrose was not due to its laevulose fraction, was suggested

from the fact that the absorption of laevulose is slower than that of dextrose (4). Proof that it was not a contributing factor was the fact that when laevulose was administered it had no effect whatever upon the blood sugar during the five-minute period of the test.

The combined data thus suggested that hydrolysis of sucrose in the human body yields something other than dextrose and laevulose which, when absorbed, is very rapidly converted into dextrose or into some other compound with similar reducing properties and similar physiological effects. Also, because of the very rapid action, it appeared that this product need not pass into the intestines before absorption, but, like ethyl alcohol, is capable of passing directly through the wall of the stomach into the general circulation. Whether dextrose is or is not absorbed by the stomach is still debatable; but that this was irrelevant here seemed clear from the fact that the effects of sucrose were more rapid than those of dextrose. It is also to be noted that in the experiments which suggested that dextrose may be absorbed by the stomach (5) the "absorption" occurred only with concentrations far greater than those used here. In view of the fundamental importance of these findings from the standpoint of the intermediate metabolism of carbohydrates, it was, therefore, considered advisable to extend this study to a larger group of cases.

SELECTION OF SUBJECTS

As in the first investigation, this report is restricted to the cases in which recovery from the excess insulin was noted within five minutes after administration of the sugar. The others are of no interest here. Including the first ten cases (1), the different forms of sugar administered and the number of tests with each form were as follows

Sugar	No.
Dextrose - - - - -	11
Laevulose - - - - -	6
Dextrose + Laevulose - - - -	6
Sucrose - - - - -	15

As in the first study, evidence of absorption of the sugar administered was not regarded as positive unless the increase of blood sugar noted was in excess of 10 mgms. per 100 cc. The combined results are shown in Table I.

DISCUSSION OF RESULTS

It will be noted that an increase of blood sugar was noted within one minute in two tests and, in both, it was due to sucrose. Of the three increases noted within two minutes, two were due to sucrose, and, of the ten in which an increase of blood sugar occurred within three minutes, six were due to sucrose. The effects of laevulose were practically negligible. The effects of the mixture of dextrose and laevulose were essentially the same as those with dextrose alone; of the eleven tests with dextrose, an increase of blood sugar was noted within three minutes in three cases

TABLE I

Percentage Incidence of Recovery from Mild Insulin Hypoglycaemia Following Ingestion of Different Sugars in Relation to Time

SUGAR	Minutes After Ingestion of Sugar										
	Total	1		2		3		4		5	
	No.	No.	%	No.	%	No.	%	No.	%	No.	%
Dextrose	11	0	0	1	9.1	2	18.2	3	27.2	5	45.4
Laevulose	6	0	0	0	0	0	0	0	0	0	0
Dextrose + Laevulose	6	0	0	0	0	2	33.3	3	50.0	1	16.6
Sucrose	15	2	13.3	2	13.3	6	40.0	4	26.6	1	6.6

an incidence of 27.3% — and, of the six with the mixture of dextrose and laevulose, an increase was noted within three minutes in two cases — an incidence of 33.3%. Comparing dextrose with sucrose, however, it will be noted that, whereas three only of the eleven tests with dextrose showed an increase of blood sugar within three minutes, ten of the fifteen treated with sucrose showed an increase within the same period — an incidence of 66.6%.

The average blood sugar time curve obtained with each of the above-mentioned sugars is graphically recorded in Chart 4, and, in Chart 5, are graphically re-

corded the average blood sugar time curves obtained with dextrose and sucrose in five cases in which the subjects were allowed to have mild reactions so as to compare the effects of dextrose with those of sucrose in the SAME individuals. It will, again, be noted that sucrose produced a more rapid and a more marked increase of blood sugar than dextrose.

KATHEROMETER EXPERIMENTS

The combined data fit in with the observation first made many years ago by Higgins (6) and repeatedly confirmed by Deuel (7), Carpenter (8) and others that sucrose increases the respiratory quotient more rapidly than dextrose. An observation with the kathrometer (9), which permits determination of the concentration of CO₂ in expired air at one-minute intervals, is of interest here. In Chart 6 are shown the percentage increases of the concentration of CO₂ in expired air at one-minute intervals following ingestion of dextrose and of sucrose. In each experiment, in order to avoid artefacts, the sugar was not administered until the recovery from the usual initial hyperventilation due to the abnormal breathing was complete. It will be noted that the increase of the concentration of CO₂ occurred earlier and reached a higher level with sucrose than with dextrose. Whether

FIGURE IV

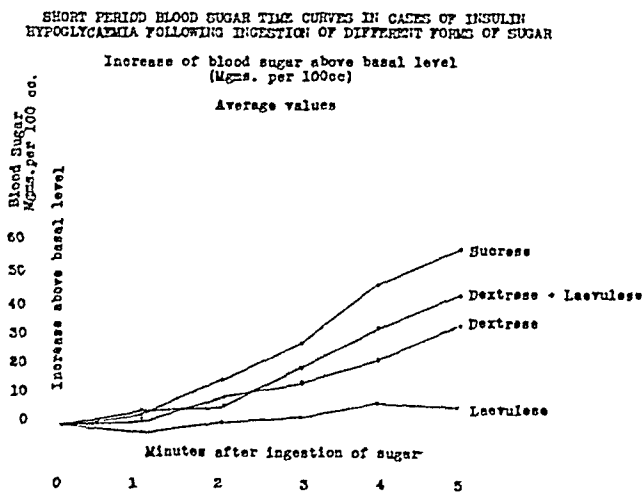


FIGURE V

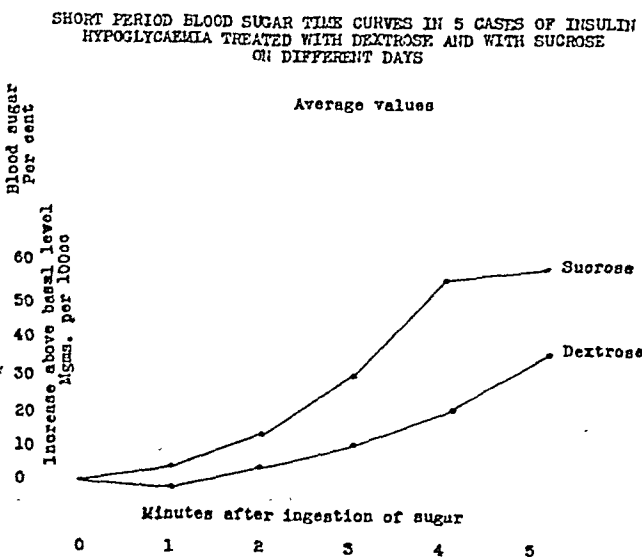
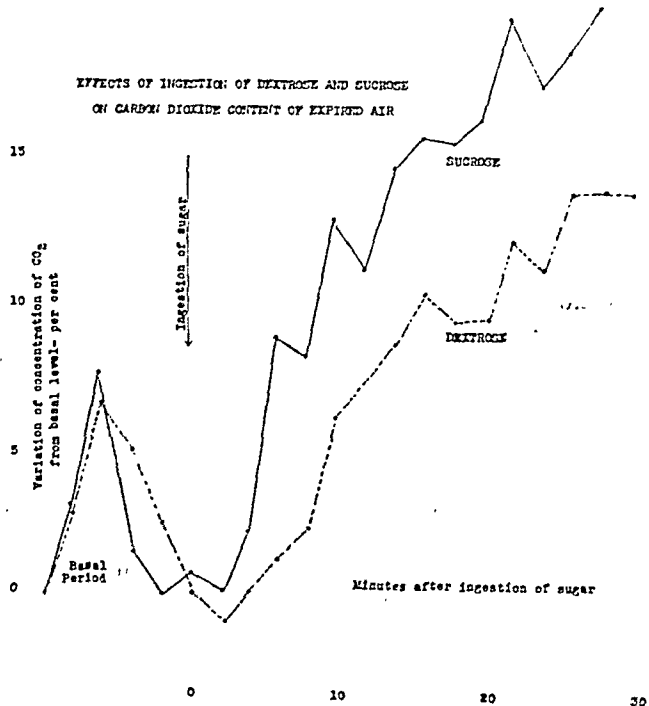


FIGURE VI

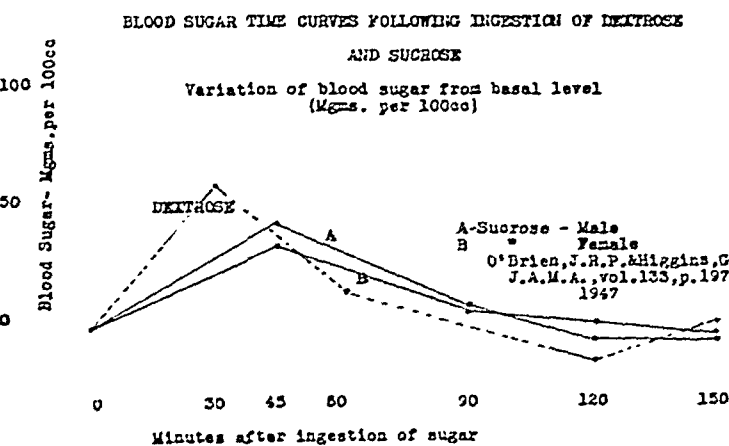


the increase was due to combustion of sugar, synthesis of fat or a lactic acid-formation is irrelevant here. The significant fact is that the increase was noted sooner with sucrose than with dextrose, and sucrose cannot have this effect until some product of its hydrolysis has been absorbed from the alimentary tract.

STANDARD BLOOD SUGAR TIME CURVES FOLLOWING INGESTION OF SUCROSE IN NORMAL INDIVIDUALS

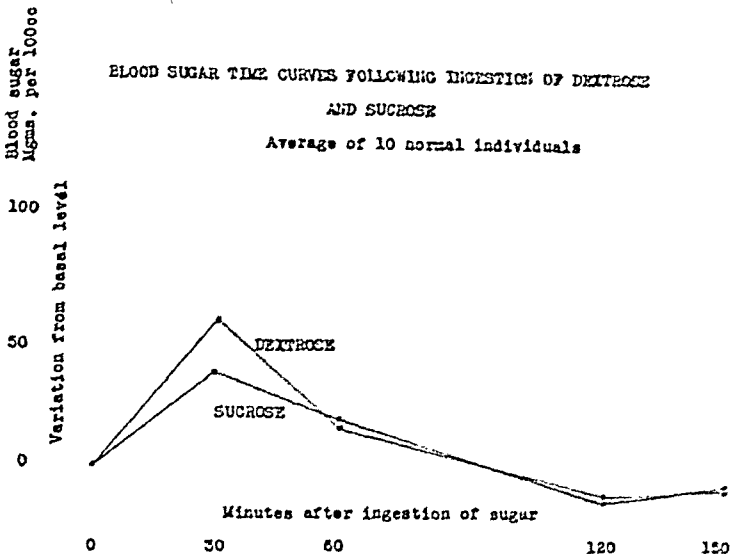
Though the effects of dextrose and of other sugars (laevulose, galactose, pentose, etc.) upon the blood sugar are well known, it is a remarkable fact that, in the vast literature on carbohydrate metabolism, the references to sucrose are extremely scanty (10, 11, 12, 13, 14, 15). Schmidt, Eastland and Burns (13) found the pattern with sucrose was essentially the same as with dextrose. Sucrose did not, however, increase the blood sugar as much as did dextrose. The findings of O'Brien and Higgins (15) were essentially the same. The average blood sugar time curves obtained with sucrose by the latter authors are graphically recorded in Chart 7. It will be noted that, whereas, the average peak of the curve with dextrose is between 0.160 and 0.180 per cent (see dotted line), with sucrose the average peak was at 0.123 per cent

FIGURE VII



in males and at 0.110 per cent in females. The data are, however, not strictly comparable, since, in the standard "sugar tolerance test" with dextrose, the first blood sample after the ingestion of the dextrose is obtained at the end of thirty minutes; whereas, in the above observations made with sucrose, the blood was not collected until the end of forty-five minutes. The data of Schmidt, Eastland and Burns (13) are still less comparable with the standard test, since the first blood sample after ingestion of the sugar was not collected until the end of one hour. Therefore, in order that the data may be strictly comparable, blood sugar time curves were obtained in ten normal individuals following ingestion of 50 grams of sucrose and the results were compared with those obtained in the same individuals with the same amount of dextrose. In each case, the blood was examined before and 30, 60, 120 and 150 minutes after ingestion of the sugar. The comparative curves are graphically recorded in Chart 8, and, again, it will be noted that sucrose is more readily utilized than dextrose.

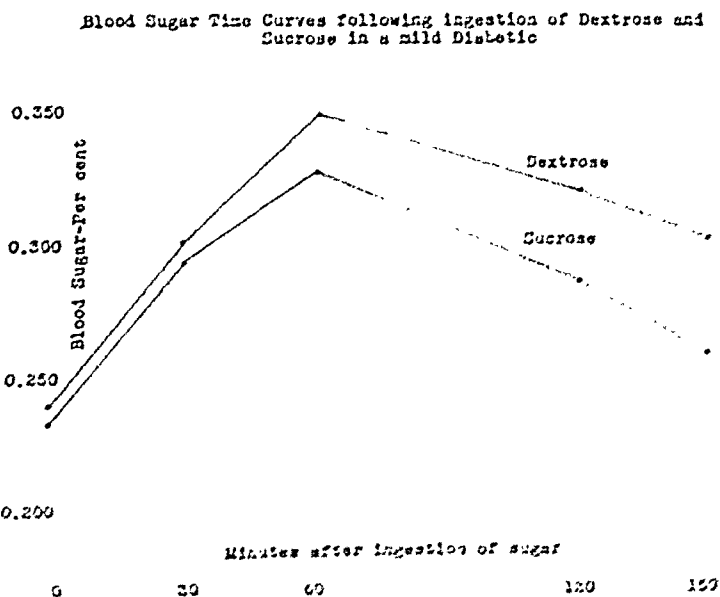
FIGURE VIII



STANDARD BLOOD SUGAR TIME CURVES FOLLOWING INGESTION OF SUCROSE IN DIABETICS

In view of the above observations in normal individuals, a similar study was made in diabetics, and that sucrose is utilized more readily than dextrose by the diabetic also is seen in Chart 9 in which are recorded the average blood sugar time curves obtained in ten mild diabetics. The data fit in with the early observation by Allen on the effects of different forms of carbohydrates in partially depancreatized animals (16). Allen found that animals, progressing towards complete recovery from early diabetes on a starch diet, could be sent into hopeless diabetes by admixture with dextrose. To Allen it seemed that the different effects of the different forms of carbohydrate were due to different rates of absorption from the alimentary

FIGURE IX



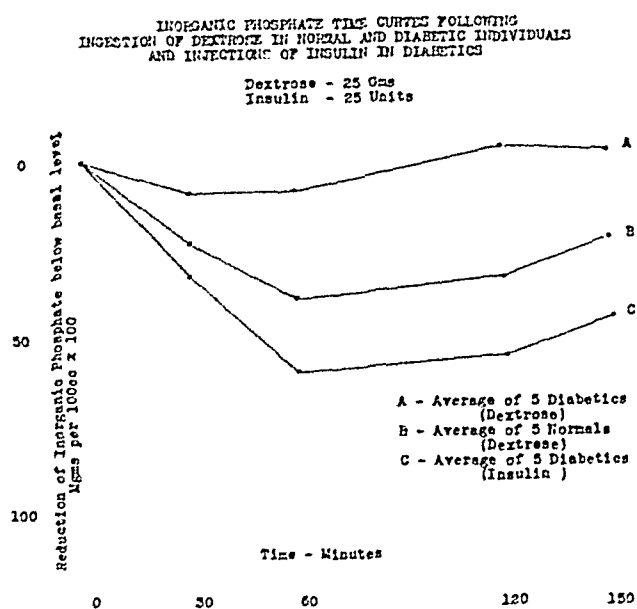
tract. That this is not the only reason is, however, now clear from the above-mentioned blood sugar studies at one-minute intervals. Suggestive also is the observation that definitely more sucrose than dextrose can be tolerated in depancreatized dogs with the same dose of insulin (17), though apparently temporarily

only (18). More significant, however, are the experiences in man. Joslin (19) has shown that, in a mild diabetic, following administration of sucrose, the respiratory quotient rises to as high a level as in normal subjects.

EFFECTS OF DIFFERENT SUGARS ON INORGANIC SERUM PHOSPHATE

It has long been known that phosphates play an important part in the metabolism of carbohydrates. In normal individuals, following ingestion of dextrose, the inorganic phosphate content of the blood is reduced; whereas, as the writer has shown, in the severe diabetic (20), in whom the utilization of carbohydrates is markedly impaired, there may be little or no change. Following administration of insulin, accompanying the fall in the blood sugar, the reduction of the inorganic phosphate content of the blood may be greater than that noted in normal individuals following administration of dextrose. This is shown in Chart 10.

FIGURE X



That different sugars affect the metabolism of inorganic phosphates differently is suggested from the more marked reduction noted by the writer with dihydroxyacetone than with dextrose, both in the normal and diabetic individual (20). This is shown in Chart 11.

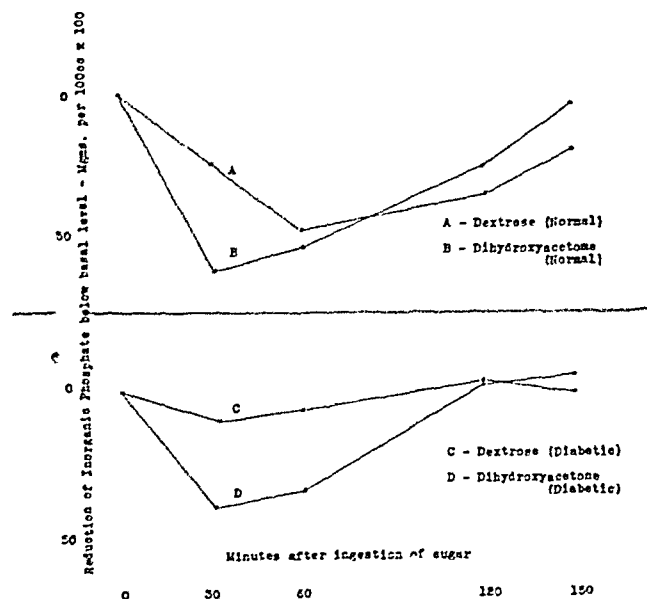
In view of these findings, an attempt was made to determine the extent to which, if any, sucrose differs from that of dextrose alone, laevulose alone, and a mixture of dextrose and laevulose in its effects upon the inorganic phosphate content of the blood.

SELECTION OF SUBJECTS

Medical students were selected as the normal subjects. In each case, conditions that are known to disturb carbohydrate metabolism (upper respiratory infections, etc.) were excluded as much as possible. A family history of diabetes was also excluded, in view of the heredity tendency of the disease. Also, in order

FIGURE XI

INORGANIC PHOSPHATE TIME CURVES FOLLOWING INGESTION OF DEXTROSE AND DIHYDROXYACETONE IN NORMAL AND DIABETIC INDIVIDUALS
(Average of 5 individuals)



to exclude possible disturbances of carbohydrate metabolism on the day of the test, sugar estimations were also made on the same blood sample.

TECHNICAL

All observations were commenced in the strictly fasting state, and no exercise was allowed during the tests, because of its known effects on carbohydrate metabolism. Smoking was also not allowed for the same reason (21).

Because of the possibility of the occurrence of minute differences only between the different sugars administered, it was necessary to consider all of the possible variables both in the collection of the blood samples and in the phosphate determinations which might account for such small differences — possible hydrolysis of organic phosphates due to delay in separation of red blood cells from plasma; hydrolysis of organic phosphates in serum compared with hydrolysis in plasma; effects of anti-coagulants (oxalates, citrates etc.) and excess quantities of molybdic acid and hydroquinone on colour developments, etc. (22, 23, 24). The method finally adopted was use of serum rather than plasma, and determination of the phosphate values with the least possible delay. Otherwise, the technique was the Briggs modification (23) of the Bell and Doisy procedure (22), and use of the photoelectric cell rather than the ordinary colorimeter for measurement of minute differences of colour. With these precautions, quantitative recovery of added phosphate was very satisfactory, that is, with an average error of 2.5%.

With the above precautions, serum inorganic phosphate time curves were obtained following ingestion of different forms of sugar. Those of particular interest here are the 150 curves with (a) dextrose, (b) laevulose, (c) sucrose and (d) a mixture of dextrose

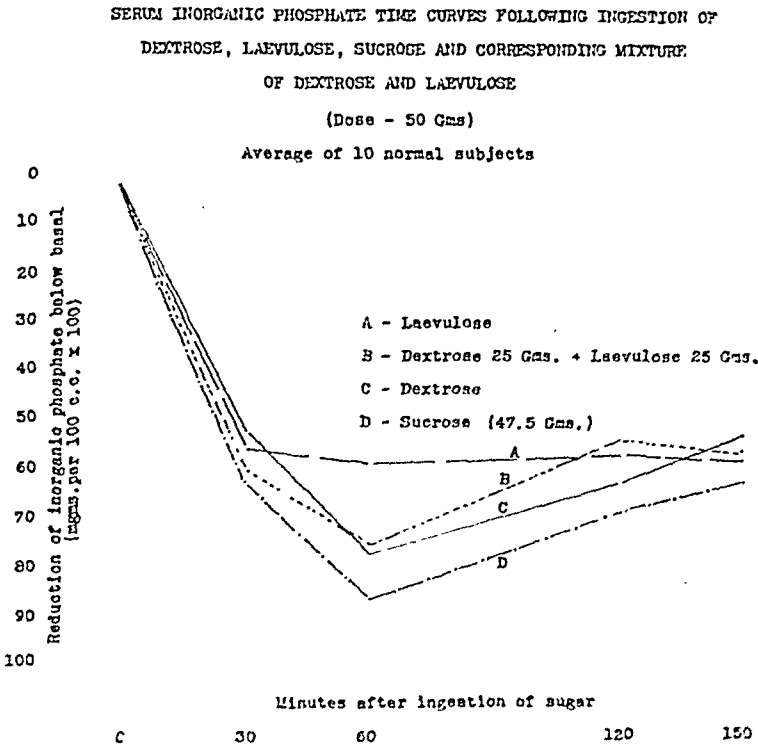
and laevulose corresponding to the amount of sucrose.
Thus:

SUGAR	Amt. (Gms.)	Number
Dextrose	50	35
Dextrose	100	35
Laevulose	50	17
Sucrose	47.5	16
Sucrose	95.0	20
Dextrose + Laevulose ..	25 (each)	15
Dextrose + Laevulose ..	50 (each)	12

DISCUSSION OF RESULTS

The average curve obtained with each of these sugars is graphically recorded in Chart 12. For strict comparability, the data include those only which were obtained with the same amount of sugar, that is, 50-gram doses of dextrose, laevulose and sucrose, and in the case of the mixed sugars, 25 grams of dextrose and 25 grams of laevulose.

FIGURE XII

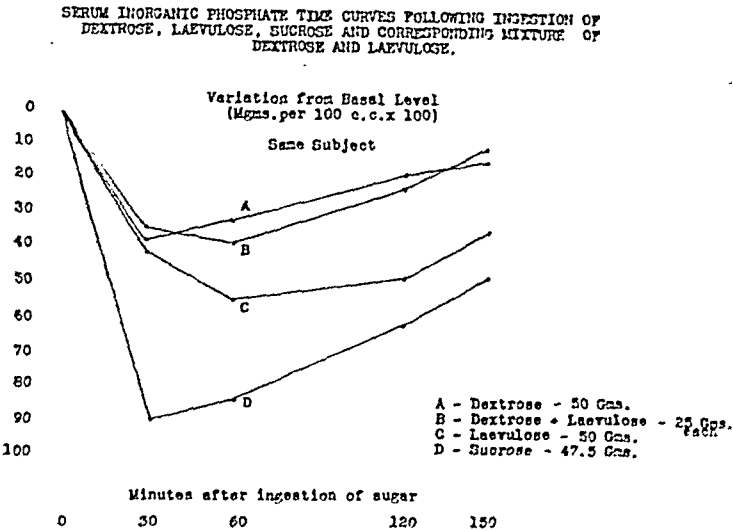


It will be noted that the most marked reduction of the inorganic phosphate content of the blood serum was obtained with sucrose. An interesting finding is that, though, compared with dextrose, laevulose has very little effect upon the sugar content of the blood, its effects upon inorganic phosphate were approximately the same as those of dextrose.

Though each of the above curves was based upon observations in ten individuals, the latter were selected at random. More significant, therefore, are the effects of the different sugars in the same individual. In Chart 13 are, therefore, graphically recorded the findings with the same amounts of all of the four sugars in the same subject, and, again, it will be noted that the most marked depression of the inorganic phosphate content of the serum was noted with sucrose.

As stated, all of the above comparisons were made with 50-gram doses of sugar (sucrose — 47.5 gms.). In Chart 14 are graphically recorded the average curves of three individuals who had received 95.0 grams of sucrose and a mixture of 50 grams of dextrose

FIGURE XIII

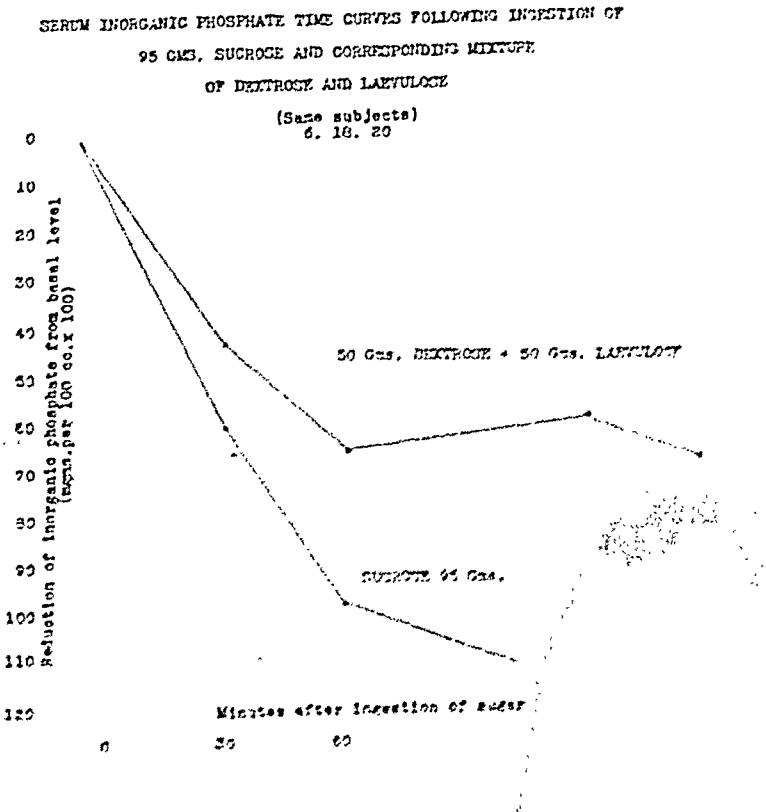


and 50 grams of laevulose. Again, it will be noted that sucrose produced a more marked reduction of the inorganic phosphate content of the blood serum than dextrose.

Combining all of the findings, the data clearly indicate that the metabolism of sucrose cannot be accounted for entirely by the metabolism of dextrose and of laevulose. The observations of Bacon, Baldwin and Bell (25) are of interest here. These authors have found that sucrose produces a different form of glycogen than that produced by glucose or fructose; whereas, glucose and fructose, whether administered intravenously or orally, produce a 12 glucose-unit of glycogen, sucrose produces an 18 glucose-unit of glycogen.

Prompted by these findings, an attempt is now being made to isolate the product or products of hydrolysis of sucrose by analysis of gastric contents at one-minute intervals following administration of sucrose solutions in human subjects. It would be premature to comment at any length upon the experiences to date. Suffice it

FIGURE XIV



to say that gastric contents, examined at one-minute intervals, following administration of sucrose in normal individuals, yield, in addition to dextrose and laevulose, substances of as yet unknown composition. The combined data thus support the observation of Higgins (6), in 1916, that "there is a fundamental and distinct difference in the metabolism of the various sugars in man and from a nutritional point of view we must recognize the possible necessity of differentiating between their action and use."

Of interest also was the finding that, in most cases, though, normally, the blood sugar reaches its peak within 30 minutes after ingestion of sugar, the maximum reduction of the inorganic phosphate content of the blood did not occur until after an hour or more. This is shown in Table 2. It will be noted that, in 20 of the 40 strictly comparable curves, the maximum depression was noted at the end of one hour. In 13, the maximum reduction occurred at the end of two hours. The significance of this difference between blood sugar and blood phosphates is not as yet known.

TABLE II

Showing Incidence of Occurrence of Maximum Reduction of Serum Inorganic Phosphate in Relation to Time, Following Ingestion of Dextrose, Laevulose, Sucrose and Corresponding Mixture of Dextrose and Laevulose

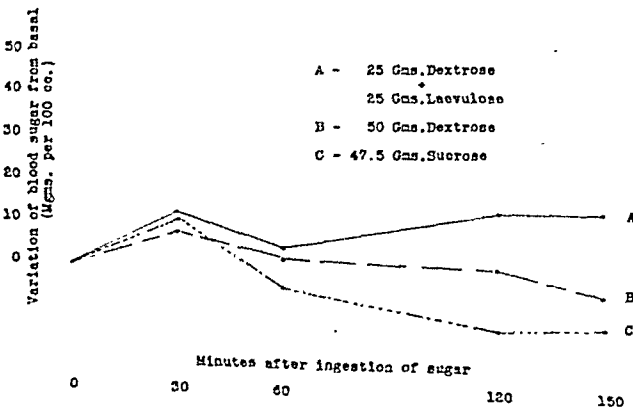
Time	Dextrose No.	Laevulose No.	Sucrose No.	Dextrose + Laevulose	TOTAL No.
30 min	1	4	0	1	6
60 min	8	0	5	7	20
120 min	1	5	5	2	13
150 min	0	1	0	0	1

PRACTICAL OBSERVATION

As is well known, blood sugar time curves are employed for a variety of diagnostic purposes, particularly for early detection of diabetes mellitus. Not infrequently, however, the curve may be almost completely flat, suggesting either defective absorption of the sugar from the alimentary tract or extremely rapid removal of the sugar from the blood. The usual practice in such cases is to repeat the test. At times, however, the result is the same. The tendency towards flat

FIGURE XV

SHOWING TENDENCY IN SAME PERSON TOWARDS FLAT OR NEARLY FLAT BLOOD SUGAR TIME CURVES REGARDLESS OF TYPE OF SUGAR INGESTED



curves in the same individual, regardless of the type of sugar ingested, is shown in Chart 15. In this study, there were 10 such flat or nearly flat curves (see Table 3). It will be noted, however, that, without exception, though there was little or no increase of blood sugar, there was a definite reduction of the concentration of

TABLE III

Showing Reduction of Serum Inorganic Phosphate with Flat Blood Sugar Time Curves Following Ingestion of Different Sugars

Subject No.	Sugar*	Test**	Basal Level	Minutes after ingestion of sugar				Maximum depression of P (Mgm. per 100 cc. x 100)
				30	60	120	150	
5	D + L/25	S	106	124	102	100	100	75
		P	360	295	285	305	305	
	D/50	S	102	110	104	100	94	45
		P	405	360	365	400	390	
6	S/47.5	S	98	110	98	82	82	65
		P	395	350	—	330	360	
	D + L/50	S	100	112	90	112	112	55
		P	415	385	360	365	360	
12	S/95	S	94	120	112	84	84	85
		P	410	325	325	390	370	
	D + L/25	S	94	126	106	108	102	55
		P	410	360	360	355	390	
13	Honey	S	94	120	86	90	96	50
		P	245	215	195	220	220	
	D/50	S	112	124	90	92	90	50
		P	290	260	240	270	270	
16	D + L/25	S	88	124	98	78	90	45
		P	315	300	270	305	280	
18	S/95	S	88	92	96	88	88	95
		P	345	265	260	250	280	

*D/50 — 50 gms. Dextrose
S/47.5 — 47.5 gms. Sucrose
S/95 — 95 gms. Sucrose
D + L/25 — 25 gms. Dextrose + 25 gms. Laevulose
D + L/50 — 50 gms. Dextrose + 50 gms. Laevulose
**S — Blood sugar, mgms. per 100 cc.
P — Serum Inorganic Phosphate, mgms. P per 100 cc. x 100

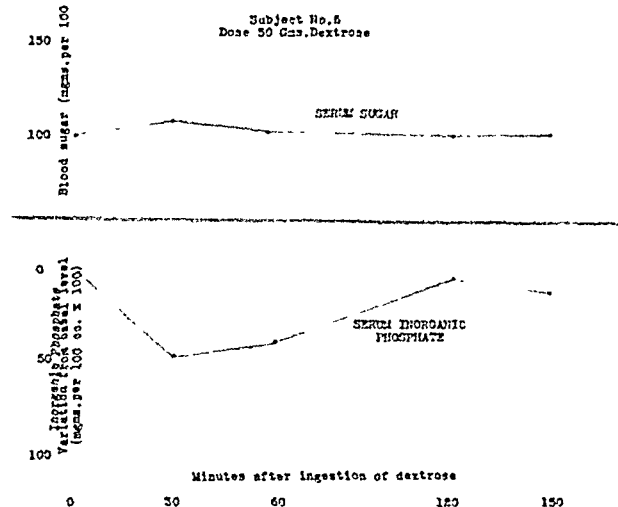
the inorganic phosphate, which clearly indicated that the absence of hyperglycaemic response to the ingestion of the sugar was not due to defective absorption of the sugar from the intestinal tract, but to an exceptionally good mechanism of storage. A typical example is graphically recorded in Figure 16. The value of simultaneous determination of the inorganic phosphate and sugar contents of the blood is thus obvious.

SUMMARY

Blood sugar estimations at one-minute intervals in mild cases of insulin hypoglycaemia, following administration of sucrose, confirmed the previous finding that, notwithstanding the necessary preliminary hydrolysis, sucrose restores the blood sugar to the normal level very rapidly. Similar studies with dextrose, laevulose and a mixture of dextrose and laevulose which corresponded to the amount of sucrose administered showed that, in most instances, the sucrose was more rapidly effective

FIGURE XVI

SERUM SUGAR AND INORGANIC PHOSPHATE TIME CURVES
FOLLOWING INGESTION OF DEXTROSE INDICATING
UTILIZATION OF SUGAR AND NOT DEFECTIVE ABSORPTION



than dextrose. Laevulose had practically no effect. The mixture of dextrose and laevulose had, approximately, the same effect as dextrose alone.

The data fit in with the effects of sucrose and of dextrose upon the concentration of CO_2 in expired air,

measured at one-minute intervals with the katherometer.

Standard blood sugar time curves obtained with 50-gram doses of dextrose and sucrose in normal individuals showed that sucrose is more readily utilized than dextrose. Similar studies in mild cases of diabetes showed that diabetics also utilize sucrose more readily than dextrose. The data fit in with the effects of sucrose and of dextrose upon the respiratory quotient in diabetics.

Serum inorganic phosphate time curves, obtained in normal individuals, following administration of various sugars showed that the maximum reduction of the inorganic phosphate content of the blood was greater with sucrose than with dextrose alone, laevulose alone and a mixture of dextrose and laevulose which correspond to the amounts of sucrose administered. The difference was still more marked when the observations were made with the different sugars in the same individual.

Gastric contents, examined at one-minute intervals, following administration of sucrose in normal human beings, yield, in addition to dextrose and laevulose, substances of as yet unknown composition.

The combined data thus support the view that dextrose and laevulose do not alone account for the metabolism of sucrose.

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A System of Diabetic Diet Prescription for the General Practitioner

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THE ONLY JUSTIFICATION for special diets for diabetic patients rests upon the existing limitation in their ability to produce — and release — variable amounts of insulin. While a subject with a normal metabolism — a non-diabetic — can elaborate insulin within a wide range of rates to assist in the utilization or almost unlimited variations in the amounts of ingested carbohydrates, a diabetic has only a very small range of insulino-genesis, usually augmented by the fixed daily doses of insulin injected subcutaneously. Consequently, the diabetic must maintain his daily food intake within corresponding narrow ranges of variation in order to keep a normal balance between his available insulin and the food ingested.

But this does not necessarily mean that the diabetic must further restrict his enjoyment of life and of good and pleasant food! As long as he maintains his daily food intake within the range of carbohydrate equivalency established by his limited supply of insulin, there is no valid reason why he cannot enjoy an otherwise fairly normal diet.

Most methods evolved for the prescription of diets for diabetics require the use of unnecessarily complicated calculations. It is actually foolish to attempt to determine the patient's food requirements from any mathematical formula. Variations in metabolic rate, food habits, physical activities and other individual characteristics vitiate the accuracy of these calculations. On the other hand, composition of food is also very variable, depending upon climate, soil, harvesting, preserving, storing and cooking methods among other factors.

Another common practice which I have decried for many years — and I am not alone in it (11), is that of having the suffering patients weigh every portion of food they consume. Between the scales and the numerous tables of percentages they must handle, it is no wonder that so many general practitioners avoid the management of these patients and so many diabetics become discouraged and eventually abandon many precautions in the control of their condition. Surprisingly to many, but not to me, a large number of patients who disregard their lists and scales and eat vegetables at will, irrespective of the percentage of carbohydrates, show no apparent ill effects in their diabetic balance. The fact is that most diabetics tolerate at least a certain amount of variation in their carbohydrate intake and the only thing needed for their dietary control is that they be taught to remain within their own safe range, which certainly can be accomplished with much simpler, practical and realistic me-

thods than those heretofore recommended by most authorities.

Among the published systems for the calculation and prescription of the diet formulae there are many kinds, from the plans that give the patient a formula for carbohydrates, proteins and fats with the well-known lists of "food percentages" to calculate his menus (1, 2, 3, 4, 5, 6, 7) and perhaps accompany that with a course of instruction requiring several weeks of expensive hospitalization or at least attendance to outpatient services equipped with several instructors, to the "Rube Goldbergian" schools with mechanical devices of the slide rule or the gyrating discs type (8, 9) or with enormously complicated — and scaring — big charts which require considerable mathematical training on the part of the patient — not to mention the poor "G. P." who is supposed to learn — and teach his patients — all of that. Other groups yet, use a scheme of "units" or "lines" and black and red "points" or "portions" (8, 10) similar to our war-time rationing plan, but still more complicated with the needed use of scores of different food charts.

Even the best intentioned attempts at simplification of this important problem fail to avoid the need for the patient to use mathematical formulae to learn what he is to eat every day (11, 12). Practically all methods require the physician to calculate his formulae with unnecessary complication and effort. Actually, and from a very practical standpoint, food requirements for every individual should be regulated very simply according to his weight responses and clinical improvement after being on an *adequate standard observation diet* until his urine is sugar free as an average and the blood sugar at *relatively* normal levels, while administering, when required, adequate doses of insulin.

In our Outpatient Clinic (J.M.H.) we use a system of diet prescriptions devised by the author (13), which avoids all the aforementioned complexities and reduces the problem of prescribing the diet and instructing the patient to its most simple factors and requires only a few minutes time for each case. These prescriptions were published for the first time in "*The Bulletin of the Jackson Memorial Hospital*" for January 1942 and later were included by F. K. Albrecht in his book, "*Modern Management in Clinical Medicine*" (14). Letters from practitioners all over America attest to the lack of complexity and the actual practical efficiency of this system.

The method, as brought up to date through constant improvements dictated by the experience gained in its use, consists of the use of menus offering various choices of standard foods in portions easily measurable without the need for weighing, but pre-calculated as to size so as to be of uniform composition within

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average safe limits or range of error. The four basic or "standard" formulae are composed of liberal — but not excessive — amounts of carbohydrates, high — but adequate — amounts of protein and relatively low amounts of fat, the aliment usually least needed but the most easily increased when so deemed necessary. These formulae have been calculated in order to provide for weight reduction (Nos. I and II), for moderate caloric needs (No. III), and for average needs (No. IV). For larger requirements, the prescriptions are so arranged that *unlimited variations and increases may be made* in a moment with the use of no more mathematical calculation than just a few simple additions.

Each one of the four basic diet-prescriptions contains a "menu" for the Morning Meal (food items to be consumed from awakening until noon: Tables II, V, VIII, XI); the Noon-Afternoon Meal (food items to be consumed from noon to sundown: Tables III, VI, IX, XII); and the Evening Meal (food items to be consumed from sundown to bedtime: Tables IV, VII, X, XIII). In addition, for patients receiving large doses of Protamine Zinc Insulin, a fourth menu (Table XVIII) with choices for a bedtime extra feeding is available.

The items for each menu are harmonically grouped to follow the present-day eating habits of the average American. Each item gives a wide selection of choices — of the same average composition — to avoid monotony, but no calculation is needed as the size of *each* individual portion has been established in accordance with the tables of food values of the U. S. Department of Agriculture or Manufacturers' Analyses (15, 16). The average composition in carbohydrates, proteins, fats and calories, is given under each item to facilitate the calculation of easy modifications to suit each individual case. Average Composition for each meal and for the Total Daily Consumption are also listed in each diet form.

No special mention is made of vitamin and mineral contents which would only complicate matters. In these well balanced formulae, according to my estimates, all requirements established by the Food and Nutrition Board of the National Research Council (17) are fully covered, except perhaps for the fat soluble vitamins in Diets Nos. I and II, which are very low in fats, as they are intended only for temporary use in the reduction of weight in obese patients. Anyway, it has been my practice to supplement these diets with a vitamin concentrate containing slightly over the minimum requirements of all known vitamins and I strongly advise this practice in connection with the use of any restricted diets.

The following is a summary containing only the lists of item-groups and their individual average chemical contents as to carbohydrates, proteins, fats and calories as well as the total values for each meal and for each one of our four basic or Standard Diets. Total values for the Standard Diets with the added Bedtime Meal are also included, giving actually a total of eight dietary formulae for the physician to select from and which undoubtedly will cover the needs of the im-

mense majority of patients (Table I).

It is obvious that some individuals will depart from the averages and adjustments may be made in these diets much more easily than with any other form of diet prescription that I know. For instance, in the case of the person who can't have his noon dinner at home, most of my diets include two slices of bread at Noon for a sandwich to be made with his main protein course ("Entree," Noon-Afternoon Meals), which with his vegetables, fruit and milk, are easily available anywhere. Other instances, where religious beliefs prevent the partaking of milk and meats on the same meals are easily obviated by the advice given in the "General Instructions" of dividing each meal into a main feeding and a between-meals snack which may allow separation of meats from dairy products. Once the physician becomes familiar with the general pattern and composition of the diets, he should have no difficulty in adjusting one to any particular patient.

In addition to the four menu-sheets already mentioned, each "diet-prescription" is given to the patient with three extra lists of portions of the same average composition as those listed in the menu-sheets for "Fruits and Fruit Juices" (Table XV), "Substitutes for one Egg" (Table XVI), and "Breads, Cereals, Crackers" (Table XVII). These three lists are nothing but extensions of the lists given under the respective items in the menu-sheets, too long for inclusion within the one page considered desirable for each meal-list, but convenient in order to increase the number of choices and to give enough guaranties of sufficient defense against the monotonous menus suffered by diabetics on the average restricted diets commonly prescribed elsewhere.

A page of "General Instructions" (Table XIV), compiled with a resume of answers to questions put up by personally interviewed and instructed diabetics during the last eighteen years gives most of the information needed by the patient for the understanding and faithful application of his diet-prescription.

Finally, a "Front Page" (not included here) is used to present the general plan of the diet with spaces for the physician to fill in the value of each item and to add to the totals. This is used mainly for the instruction of the resident staff at the Hospital and is valuable for any physician to use in order to gain a good understanding of dietetic values and proficiency in the rapid calculation of the diet. Whenever the basic or standard diet formula must be modified to suit an individual case, this "front page" provides the means to fit in the changes.

The main difference between this system and all others is that in this case *we start from the formula of a normal menu to fit it to the patient's needs* which obviously is much simpler than parting from a cold mathematical formula to build three or four meals a day around it.

The following Tables are the mimeographed forms used to make up the diets at the clinic. Pages 3, 4, and 5 with the actual menus for three regular meals in each diet are the only ones that vary for the Diets Nos. I, II, III and IV. Page 5' is added only when

an extra bedtime feeding is indicated. The lists of "Bread, Cereals and Crackers" is not used in Diet No. I (for cases with marked obesity), where only English Melba Toast is allowed.

For the reader's convenience, and so that he may copy the diets for use with his patients if he so desires, all but one of the eighteen "forms" used in my Clinic are included here (Tables II to XVIII).

TABLE I

LAMAR SYSTEM of DIET PRESCRIPTIONS: SUMMARY
(Standard Diets)

DIET NO. I

		C	P	F	Cal.
Morning Meal	I—Fruits (1)	13	1	0	56
	II—Entree (1)	0	6	6	78
	III—Melba Toast (2)	9	1	0	40
	IV—Buttermilk (8 oz.)	10	6	0	64
		32	14	6	238
Noon Meal	I—Vegetable plate	13	2	0	60
	II—Entree (1)	1	13	9	137
	III—Melba Toast (2)	9	1	0	40
	IV—Buttermilk (8 oz.)	12	6	0	64
	V—Dessert (Fruit-Gelatine)	12	3	0	60
		45	25	9	361
Evening Meal	I—Entree (1)	0	20	9	161
	II—Vegetable (1)	9	1	0	40
	III—Salad	9	1	0	40
	IV—Melba Toast (2)	9	1	0	40
	V—Buttermilk (8 oz.)	10	6	0	64
	VI—Dessert (Fruit-Gelatine)	12	3	0	60
		49	32	9	405

TOTALS FOR DIET NO. I: C 126, P 71, F 24, Calories 1004

DIET NO. II

Morning Meal	I—Fruits (1)	13	1	0	56
	II—Entree (1)	0	6	6	78
	III—Bread (1)	13	2	1	69
	IV—Buttermilk (8 oz.)	10	6	0	64
		36	15	7	267
Noon Meal	I—Vegetable Plate	13	2	0	60
	II—Entree (1)	1	13	9	137
	III—Bread (2)	26	4	2	138
	IV—Buttermilk (8 oz.)	10	6	0	64
	V—Dessert (Fruit-Gelatine)	12	3	0	60
		62	28	11	459
Evening Meal	I—Soup	3	4	0	28
	II—Entree (1)	0	20	9	161
	III—Vegetable (1)	9	1	0	40
	IV—Salad	9	1	0	40
	V—Bread (1)	13	2	1	69
	VI—Buttermilk (8 oz.)	10	6	0	64
	VII—Dessert (Fruit-Gelatine)	12	3	0	60
		56	37	10	462

TOTALS FOR DIET NO. II: C 154, P 80, F 28, Calories 1188

DIET NO. III

Morning Meal	I—Fruits (1)	13	1	0	56
	II—Entree (1)	0	6	6	78
	III—Bread (2)	26	4	2	138
	IV—Milk (8 oz.)	10	6	8	136
		49	17	16	408
Noon Meal	I—Vegetable Plate	13	2	0	60
	II—Entree (1)	1	13	9	137
	III—Bread (2)	26	4	2	138
	IV—Milk (8 oz.)	10	6	8	136
	V—Dessert (Fruit-Gelatine)	12	3	0	60
		62	28	19	531

Evening Meal	I—Soup	3	4	0	28
	II—Entree (1)	0	20	9	161
	III—Vegetable (1)	9	1	0	40
	IV—Salad	9	1	0	40
	V—Bread (2)	26	4	2	138
	VI—Milk (8 oz.)	10	6	8	136
	VII—Dessert (Fruit-Gelatine)	12	3	0	60
		69	39	19	603

TOTALS FOR DIET NO. III: C 180, P 84, F 54, Calories 1542

DIET NO. IV

Morning Meal	I—Fruits (1)	13	1	0	56
	II—Entree (2)	0	12	12	156
	III—Bread (2)	26	4	2	138
	IV—Butter (1)	0	0	7	63
	V—Milk (8 oz.)	10	6	8	136
		49	23	29	549
Noon Meal	I—Vegetable plate	13	2	0	60
	II—Entree (1)	1	13	9	137
	III—Bread (2)	26	4	2	138
	IV—Butter (1)	0	0	7	63
	V—Milk (8 oz.)	10	6	8	136
	VI—Dessert (Fruit-Gelatine)	12	3	0	60
		62	28	26	594
Evening Meal	I—Soup	3	4	0	28
	II—Entree (1)	0	20	9	161
	III—Vegetable (1)	9	1	0	40
	IV—Salad	9	1	0	40
	V—Butter (1)	0	0	7	63
	VI—Bread (2)	26	4	2	138
	VII—Milk (8 oz.)	10	6	8	136
	VIII—Dessert (Sherbet)	24	6	0	120
		81	42	26	726

TOTALS FOR DIET NO. IV: C 192, P 93, F 81, Calories 1869

Bedtime Meal average consumption: C 25, P 8, F 16, Cal. 276

Summary of Totals for all Four Standard Diets:

No. I — C 126, P 72, F 24, Calories 1008
No. II — C 154, P 80, F 28, Calories 1188
No. III — C 180, P 84, F 54, Calories 1542
No. IV — C 192, P 93, F 81, Calories 1869

Totals for Standard Diets plus Bedtime Meal Added:

No. I — C 151, P 80, F 40, Calories 1284
No. II — C 179, P 88, F 42, Calories 1464
No. III — C 205, P 92, F 70, Calories 1818
No. IV — C 217, P 101, F 97, Calories 2145

Innumerable variations may be made by increasing or decreasing the portions of the different items, the values of which are all shown through the diet prescription lists.

TABLE II

Page 3 for Diet I

LAMAR DIET PRESCRIPTION NO. I

Average Composition of this Diet per day. Carbohydrates 126 gm, Proteins 71 gm, Fats 24 gm, Calories 1004

MORNING MEAL I (To eat from Awakening to Noon)

I. FRUITS: (Choice of ONE Portion)

Apple, fresh or baked, no sugar: One small (2 1/2")
Applesauce, no sugar: Two-thirds cup
Banana, peeled: 2/3 of a small one or 1/2 large
Cantaloupe: 1/2 of a 5" melon or 1/2 cup diced
Dates, dried: Two, medium sized
Figs, breakfast type, canned: 1/4 cup scant, no juice
Fruit cocktail, canned: 1/4 cup scant, no juice
Grapefruit: One-half large to two-thirds small
Grapes, green, seedless: One bunch, average 50
Honeydew melon: One-third of a 5" melon
Mangoes, Florida: Two-thirds of a small mango
Olives, green (high in fat content): 4 medium size
Orange: One, small to medium size
Papaya, fresh: One small serving (1/2 cup diced)

Peaches, fresh: One, medium large
Pears, fresh: One, medium small
Pineapple: One-half to two-thirds cup, diced
Plums, fresh: Three, medium sized
Strawberries, fresh: Fifteen large berries
Tangerines: One large or two small ones
Watermelon: One cup, cubes or balls, red portion

or JUICES:

Apple juice: One-half cup or four ounces
Grapefruit juice, unsweetened: Five ounces
Orange juice, unsweetened: Four ounces (1/2 cup)
Pineapple juice: One-half cup, scant (3 1/2 ounces)
Tomato juice: One full cup or eight ounces
or any ONE Portion from the additional list of Fruits
and Juices on back pages of this Diet.
(C 13, P 1, F 0, Calories 56)

II. ENTREE: (Choice of ONE Portion)

Egg, poached, boiled, no fat used in cooking: One Bacon,
very crisp, all fat drained: Four strips Beef roast, me-
dium fat: One slice 2" x 4" x 1/2"; Cheese, American:
One cube 1" x 1" x 1"; Chicken livers: 1/4 cup with 1/2
pat of butter; Ham, smoked, lean: One slice 2" x 1 1/2"
x 1 1/2"

or any ONE Portion from the list of Additional Sub-
stitutions for one Egg on back pages of this Diet

(C 0, P 6, F 6, Calories 78)

III. ENGLISH MELBA TOAST: Two pieces
(C 9, P 1, F 0, Calories 40)**IV. BUTTERMILK or SKIM MILK: Eight Ounces**
(C 10, P 6, F 0, Calories 64)**V. COFFEE, SANKA or TEA: See "General Instructions"**

AVERAGES FOR THIS MEAL: C 32, P 14, F 6, Cal. 238

TABLE III

Page 4 for Diet I

LAMAR DIET PRESCRIPTION NO. I**NOON-AFTERNOON MEAL I (To eat from Noon to
Sundown)****I. VEGETABLE PLATE:**

Prepared with any of the following in large, generous
amounts, all you wish, raw or steamed, fresh, frozen or
waterpack canned vegetables, Lemon or lime juice, vine-
gar, salt, pepper and other condiments in moderation. No
sauces or gravies, but mineral oil dressing may be used
if desired:

Asparagus, Dock, Romaine, Bamboo shoots, Eggplant,
Sauerkraut, Beet leaves, Endive, Seakale, Broccoli, Fennel,
Sorrel, Brussel sprouts, Lettuce, Spinach, Cabbage, Mush-
rooms, Summer Squash, Cauliflower, Mustard greens,
Green String beans, Celery, Okra, Wax String beans,
Chard, Purslane, Swiss chard, Chicory leaves, Radishes,
Tomatoes, Cucumbers, Rhubarb, Watercress.

Tomato juice, up to 1/2 cup only (4 oz.).

(C 13, P 2, F 0, Calories 60)

II. ENTREE: (Choice of ONE Portion)

American cheese: One piece 2" x 3" x 1/2"
Brick cheese, Kraft: 3/16" slice from a 5-lb. loaf
Cottage cheese, plain: 1/4 cup and One pat Butter
Codfish, boneless, salted: One piece 4" x 2" x 1/2"
Crabmeat, canned or fresh: 1/2 cup and 1 pat butter
Eggs: Two, cooked in any way using no extra fat
Frankfurter: One of average size
Halibut or any lean fish: Two steaks 3" x 2" x 1/2"
Liver, broiled: 1 slice 4" x 2" x 1/2" and 3 strips bacon
Lobstermeat, boiled or broiled: 1/2 cup and one pat butter
Oysters, fresh: 1/4 cup (4 to 6) and 1/2 cup whole milk
Salmon, canned: One-half cup and one-half pat butter
Shrimp, fresh or canned: 8 large and 1/2 pat butter
Tuna fish, canned, oil drained: One-quarter cup
(C 1, P 13, F 9, Calories 137)

III. ENGLISH MELBA TOAST: Two pieces
(C 9, P 1, F 0, Calories 40)**IV. BUTTERMILK or SKIM MILK: Eight ounces**

(C 10, P 6, F 0, Calories 64)

V. DESSERT:

Choice of ONE Portion of any Fruit listed for the Morn-
ing Meal or in the additional List of Fruits and Juices,
prepared with D-Zerta or with plain gelatine sweetened
with saccharin, if desired.

(C 12, P 3, F 0, Calories 60)

VI. COFFEE, SANKA or TEA: See "General Instructions"

AVERAGES FOR THIS MEAL: C 45, P 25, F 9, Cal. 361

TABLE IV

Page 5 for Diet I

LAMAR DIET PRESCRIPTION NO. I**EVENING MEAL I (To eat from Sundown to Bedtime)****I — ENTREE (Choice of ONE Portion)**

All meats must be free from visible fat and cooked
without fat unless specifically allowed. (One pat butter
equals 1/2 tablespoon fat). No sauces or gravies but
vinegar, salt and other condiments may be used moder-
ately. Amounts are roughly the same as 1/4 lb. por-
tions as bought, then trimmed of all fat and inedible
parts. Edible portions are about 100 gm.

Beef, boiled, broiled, roast: Two slices 4" x 2" x 1/2" each;
Beef, hamburger, lean: Two patties made from 2" balls;
Chicken, roast, breast: Three slices 3" x 4" x 1/2" each;
Chicken, young, boiled or broiled: One-half, medium size;
Fish, lean, baked, broiled: Two slices 3" x 3" x 1/2" each;
Ham, lean, baked, broiled: Two slices 4" x 3" x 1/4" each;
Lamb chops, lean, broiled: Two, 3" x 2" x 1/2" each;
Lamb leg, roast: Two slices 4" x 2" x 1/2" each;
Liver, broiled: A steak 3" x 5" x 1/2" & 3 strips bacon;
Pork chops, lean, broiled: Two small chops;
Pork leg, roast: One slice 4" x 2" x 1/2";
Turkey breast, roast: Two slices 6" x 3" x 1/2" each;
Turtle: A broiled steak 4" x 3" x 3/4" and one pat butter;
Veal chop, broiled: One medium-sized chop;
Veal cutlets, broiled: Two, 4" x 2" x 1/2" each;
Veal roast, cold: Two slices 3" x 2" x 1/2" each.

(C 0, P 20, F 9, Calories 161)

II — VEGETABLES: (Choice of ONE Portion)

Beans, Lima, fresh, frozen or canned: One-third cup,
Beans, Navy and others: One-half cup, boiled;
Beets, boiled: One-half to two-thirds cup;
Carrots, raw or cooked: One-half to two-thirds cup;
Onions, white or yellow: One-half cup;
Parsnips: One-third cup;
Peas, green, canned: One-half cup;
Peas, green, shelled, fresh or frozen: One-third cup;
Potato, baked or boiled: One, size of a large hen egg;
Rice, steamed, white: One-third cup;
Rutabagas: One-third to three-quarters cup;
Squash, winter, cooked, fresh or canned: One-half cup;
Turnips, root, white, cooked or raw: 1/2 to 2/3 cup diced;
or TWO generous portions of Noon Meal Vegetables

(C 9, P 1, F 0, Calories 40)

**III — SALAD: Made from TWO generous portions from
the Noon Meal Vegetables or from ONE from above list.**
(C 9, P 1, F 0, Calories 40)**IV — ENGLISH MELBA TOAST: Two pieces**

(C 9, P 1, F 0, Calories 40)

V — BUTTERMILK or SKIM MILK: Eight ounces
(C 10, P 6, F 0, Calories 64)**VI — DESSERT: Choice of ONE portion of any fruit
listed for the Morning Meal or in the additional List of
Fruits and Juices, prepared with D-Zerta plain gelatine
and sweetened with saccharine if desired.**
(C 12, P 3, F 0, Calories 60)**VII—COFFEE, SANKA or TEA: See "General Instructions"**

AVERAGES FOR THIS MEAL: C 49, P 32, F 9, Cal. 405

TABLE V

Page 3 for Diet II

LAMAR DIET PRESCRIPTION NO. II

Average composition of this diet per day: Carbohydrates 154 gm., Proteins 80 gm., Fats 28 gm., Calories 1188.

MORNING MEAL II (To eat from Awakening to Noon)

I — FRUITS: (Choice of ONE Portion)

Apple, fresh or baked, no sugar: One small (2 1/2");
Applesauce, no sugar: Two-thirds cup;
Banana, peeled: 2/3 of a small one or 1/2 large;
Cantaloupe: 1/2 of a 5" melon or 1/ cup diced;
Dates, dried: Two, medium sized;
Figs, breakfast type, canned: 1/4 cup scant, no juice;
Fruit Cocktail, canned: 1/4 cup scant, no juice;
Grapefruit: One-half large to two-thirds small;
Grapes, green, seedless: One bunch, average 50;
Honeydew melon: One-third of a 5" melon;
Mangoes, Florida: Two-thirds of a small mango;
Olives, green (high in fat content): 4 medium size;
Orange: One, small to medium size;
Papaya, fresh: One small serving (1/2 cup diced);
Peaches, fresh: One, medium large;
Pear, fresh: One, medium small;
Pineapple: One-half to two-thirds cup, diced;
Plums, fresh: Three, medium sized;
Strawberries, fresh: Fifteen large berries;
Tangerine: One large or two small ones;
Watermelon: One cup, cubes or balls, red portion;

or JUICES:

Apple juice: One-half cup or four ounces;
Grapefruit juice, unsweetened: Five ounces;
Orange juice, unsweetened: Four ounces (1/2 cup);
Pineapple juice: One-half cup scant (3 1/2 ounces);
Tomato juice: One full cup or eight ounces
or any ONE Portion from the additional List of Fruits
and Juices on back pages of this Diet.

(C 13, P 1, F 0, Calories 56)

II — ENTREE: (Choice of ONE Portion)

Egg, poached, boiled, no fat used in cooking: One;
Bacon, very crisp, all fat drained: Four strips;
Beef roast, medium fat: One slice 2" x 4" x 1/2";
Cheese, American: One cube 1" x 1" x 1";
Chicken livers: 1/4 cup with 1/2 pat of butter;
Ham, smoked, lean: One slice 2" x 1 1/2" x 1/2"

or any ONE Portion from the List of Additional Substitutions for One Egg on back pages of this diet

(C 0, P 6, F 6, Calories 78)

III — BREAD or CEREAL: Wheat or White, One Slice or any ONE Portion from the additional List of Breads, Cereals and Crackers

(C 13, P 2, F 1, Calories 69)

IV — BUTTERMILK or SKIM MILK: One 8-ounce glass

(C 10, P 6, F 0, Calories 64)

V — COFFEE, TEA or Sanka: See "General Instructions"

AVERAGES FOR THIS MEAL: C 36, P 15, F 7, Calories 267

TABLE VI

Page 4 for Diet II

LAMAR DIET PRESCRIPTION NO. II

Noon-Afternoon Meal II (To eat from Noon to Sundown)

I — VEGETABLE PLATE: Prepared with any of the following in large, generous amounts, all you wish, raw or steamed, fresh, frozen or waterpack canned vegetables. Lemon or lime juice, vinegar, salt, pepper and other condiments in moderation. No sauces or gravies, but mineral oil dressing may be used if desired:

Asparagus, Bamboo shoots, Beet leaves, Broccoli, Brussel Sprouts, Cabbage, Cauliflower, Celery, Chard, Chicory leaves, Cucumbers, Dock, Eggplant Endive Fennel Lettuce Mushrooms, Mustard greens, Okra, Purslane, Radishes, Rhubarb, Romanine, Sauerkraut, Seakale, Sorrel, Spitchack, Summer Squash, Green String Beans, Wax Green Beans, Swiss Chard, Tomatoes, Watercress.

Tomato juice, up to 1/2 cup only (4 oz.).

(C 13, P 2, F 0, Calories 60)

II — ENTREE: (Choice of ONE Portion)

American Cheese: One piece 2" x 3" x 1/2";
Brick Cheese, Kraft: 3/16" slice from a 5 lb. loaf;
Cottage Cheese, plain: 1/4 cup and one pat butter;
Codfish, boneless, salted: One piece 4" x 2" x 1/2";
Crabmeat, canned or fresh: 1/2 cup and one pat butter;
Eggs: Two, cooked in any way using no extra fat;
Frankfurter: One of average size;
Halibut or any lean fish: Two steaks 3" x 2" x 1/2";
Liver, broiled: 1 slice 4" x 2" x 1/2" and 3 strips bacon;
Lobstermeat, boiled or broiled: 1/2 cup and one pat butter;
Oysters, fresh: 1/4 cup (4 to 6) and 1/2 cup whole milk;
Salmon, canned: One-half cup and one-half pat butter;
Shrimp, fresh or canned: 8 large and one-half pat butter;
Tunafish, canned, oil drained: One-quarter cup
(C 1, P 13, F 9, Calories 137)

III — BREAD: Wheat or White, Two slices or any TWO Portions from the additional List of Breads, Cereals and Crackers

(C 26, P 4, F 2, Calories 138)

IV — BUTTERMILK or SKIM MILK: One 8-ounce glass

(C 10, P 6, F 0, Calories 64)

V — DESSERT: Choice of ONE Portion of any Fruit listed for the MORNING MEAL or in the additional List of Fruits and Juices, prepared with D-Zerta or with plain gelatine sweetened with saccharin, if desired.

(C 12, P 3, F 0, Calories 60)

VI — COFFEE, SANKA or TEA: These have no food value. Unless otherwise instructed you may have moderate amounts at any time using no extra cream or sugar but saccharin if necessary for sweetening.

AVERAGE FOR THIS MEAL: C 62, P 28, F 11, Ca. 459

TABLE VII

Page 5 for Diet II

LAMAR DIET PRESCRIPTION NO. II

EVENING MEAL II (To eat from Sundown to Bedtime)

I — SOUP: Made with any fat-free stock, (meat, chicken, fish broth or bouillon cube) and vegetables from the Noon Meal in any amount or part of the measured vegetables allowed for this meal - - ONE CUP

(C 3, P 4, F 0, Calories 28)

II — ENTREE: (Choice of ONE Portion)

All meats must be free from visible fat and cooked without fat unless specifically allowed (One pat butter equals 1/2 tablespoon fat). No sauces or gravies but vinegar, salt and other condiments may be used moderately. Amounts are roughly the same as 1/4 lb. portions as bought, then trimmed of all fat and inedible parts. Edible portions are about 100 gm.:

Beef, boiled, broiled, roast: Two slices 4" x 2" x 1/2" each;
Beef, hamburger, lean: Two patties made from 2" balls;
Beef Tenderloin: One broiled steak 4" x 3" x 1";
Chicken, roast, breast: Three slices 3" x 4" x 1/2" each;
Chicken, young, boiled or broiled: One-half, medium size;
Fish, lean, baked, broiled: Two slices 3" x 3" x 1/2" each;
Ham, lean, baked, broiled: Two slices 4" x 3" x 1/4" each;
Lamb chops, lean, broiled: Two, 3" x 2" x 1/2" each;
Lamb leg, roast: Two slices 4" x 2" x 1/2" each;
Liver, broiled: A steak 3" x 5" x 1/2" and 3 strips bacon;
Pork chops, lean, broiled: Two small chops;
Pork leg, roast: One slice 4" x 2" x 1/2";
Turkey breast, roast: Two slices 6" x 3" x 1/2" each;
Turtle: A broiled steak 4" x 3" x 3/4" and 1 pat butter;
Veal Chop, broiled: One medium sized chop;
Veal cutlets, broiled: Two, 4" x 2" x 1/2" each;
Veal roast, cold: Two slices 3" x 2" x 1/2" each.
(C 0, P 20, F 3, Calories 161)

III — VEGETABLES: (Choice of ONE Portion)

Beans, Lima, fresh, frozen or canned: One-third cup;
Beans, Navy and others: One-half cup, boiled;
Beets, boiled: One-half to two-thirds cup;
Carrots, raw or cooked: One-half to two-thirds cup;
Onions, white or yellow: One-half cup;
Parsnips: One-third cup;

Peas, green, canned: One-half cup;
Peas, green, shelled, fresh or frozen: One-third cup;
Potato, baked or boiled: One, size of a large hen egg;
Rice, steamed white: One-third cup;
Rutabagas: One-third to three-quarters cup;
Squash, winter, cooked, fresh or canned: One-half cup;
Turnips, root, white, cooked or raw: 1/2 to 2/3 cup diced;
or TWO generous portions of Noon Meal Vegetables
(C 9, P 1, F 0, Calories 40)

IV — SALAD: Made from TWO generous portions from the Noon Meal Vegetables or from ONE from above list.
(C 9, P 1, F 0, Calories 40)

V — BREAD: Choice of any ONE Portion from the List of Breads, Cereals and Crackers.
(C 13, P 2, F 1, Calories 69)

VI — BUTTERMILK or SKIM MILK: One 8-ounce glass
(C 10, P 6, F 0, Calories 64)

VII — DESSERT: Choice of ONE Portion of any fruit listed in the Morning Meal, prepared with D-Zerta or with plain Gelatine.
(C 12, P 3, F 0, Calories 60)

VIII — COFFEE, SANKA or TEA: See "General Instructions"

AVERAGES FOR THIS MEAL: C 56, P 37, F 10, Cal 462

TABLE VIII

Page 3 for Diet III

LAMAR DIET PRESCRIPTION NO. III

Average composition of this diet per day: Carbohydrates 180 gm., Proteins 84 gm., Fats 54 gm., Calories 1542.

MORNING MEAL III: (To eat from Awakening to Noon)

I — FRUITS: (Choice of ONE Portion)

Apple, fresh or baked, no sugar: One small (2 1/2")
Applesauce, no sugar: Two-thirds cup;
Banana, peeled: 2/3 of a small one or 1/2 large;
Cantaloupe: 1/2 of a 5" melon or 1/2 cup diced;
Dates, dried: Two, medium sized;
Figs, breakfast type, canned: 1/4 cup scant, no juice;
Fruit cocktail, canned: 1/4 cup scant, no juice;
Grapefruit: One-half large to two-thirds small;
Grapes, green, seedless: One bunch, average 50;
Honeydew melon: One-third of a 5" melon;
Mangoes, Florida: Two-thirds of a small mango;
Olives, green (high in fat content): 5 medium size;
Orange: One, small to medium size;
Papaya, fresh: One small serving (1/2 cup diced);
Peaches, fresh: One, medium large;
Pear, fresh: One, medium size;
Pineapple: One-half to two-thirds cup, diced;
Plums, fresh: Three, medium sized;
Strawberries, fresh: Fifteen large berries;
Tangerines: One large or two small ones;
Watermelon: One cup, cubes or balls, red portion

or JUICES:

Apple juice: One-half cup or four ounces;
Grapefruit juice, unsweetened: Five ounces;
Orange juice, unsweetened: Four ounces (1/2 cup);
Pineapple juice: One-half cup, scant (3 1/2 ounces);
Tomato juice: One full cup or eight ounces
or any ONE Portion from the additional List of Fruits
and Juices on back pages of this Diet.
(C 13, P 1, F 0, Calories 56)

II — ENTREE: (Choice of ONE Portion)

Egg, poached, boiled, no fat used in cooking: One;
Bacon, very crisp, all fat drained: Four strips;
Beef, roast, medium fat: One slice 2" x 4" x 1/2";
Cheese, American: One cube 1" x 1" x 1";
Chicken livers: 1/4 cup with 1/2 pat of butter;
Ham, smoked, lean: One slice 2" x 1 1/2" x 1/2";
or any ONE Portion from the List of Additional Substitutions for One Egg on back pages of this Diet
(C 0, P 6, F 6, Calories 78)

III — BREAD or CEREAL: Two slices, wheat or white, or any TWO Portions from the additional List of Breads, Cereals and Crackers.
(C 26, P 4, F 2, Calories 138)

IV — MILK: Whole milk, fresh, pasteurized, homogenized, boiled or made from whole dried milk or from canned evaporated, no sugar added: Eight ounces.
(C 10, P 6, F 8, Calories 138)

V — COFFEE, SANKA or TEA: See "General Instructions"
(A pleasant combination consists of "half and half" boiled milk and coffee)

AVERAGES FOR THIS MEAL: C 49, P 17, F 16, Cal. 408

TABLE IX

Page 4 for Diet III

LAMAR DIET PRESCRIPTION NO. III

Noon-Afternoon Meal III: (To eat from Noon to Sundown)

I — VEGETABLE PLATE: Prepared with any of the following in large, generous amounts, all you wish, raw or steamed, fresh, frozen or waterpack canned vegetables. Lemon or lime juice, vinegar, salt, pepper and other condiments in moderation. No sauces or gravies, but mineral oil dressing may be used if desired:

Asparagus, Bamboo shoots, Beet leaves, Broccoli, Brussels sprouts, Cabbage, Cauliflower, Celery, Chard, Chicory leaves, Cucumbers, Dook, Eggplant, Endive, Fennel, Lettuce, Mushrooms, Mustard greens, Okra, Purslane, Radishes, Rhubarb, Romaine, Sauerkraut, Seakale, Sorrel, Spinach, Summer Squash, Green string beans, Wax string beans, Swiss chard, Tomatoes, Watercress.

Tomato juice, up to 1/2 cup only (4 oz.).

(C 13, P 2, F 0, Calories 60)

II — ENTREE: (Choice of ONE Portion)

American Cheese: One piece 2" x 3" x 1/2";
Brick Cheese, Kraft: 3/16" slice from a 5 pound loaf;
Cottage Cheese, plain: 1/4 cup and one pat butter;
Codfish, boneless, salted: One piece 4" x 2" x 1/2";
Crabmeat, canned or fresh: 1/2 cup and one pat butter;
Eggs: Two, cooked in any way using no extra fat;
Frankfurter: One of average size;
Halibut or any lean fish: Two steaks 3" x 2" x 1/2";
Liver, broiled: 1 slice 4" x 2" x 1/2" and 3 strips bacon;
Lobstermeat, boiled or broiled: 1/2 cup and 1 pat butter;
Oysters, fresh: 1/4 cup (4 to 6) and 1/2 cup whole milk;
Salmon, canned: One-half cup and one-half pat butter;
Shrimp, fresh or canned: 8 large and 1/2 pat butter;
Tuna fish, canned, oil drained: One-quarter cup.

(C 1, P 13, F 9, Calories 137)

III — BREAD: Wheat or white. two slices or any TWO Portions from the List of Breads, Cereals and Crackers on back pages of this Diet.

(C 26, P 4, F 2, Calories 138)

IV — MILK: Whole milk, one 8-ounce glass

(C 10, P 6, F 8, Calories 136)

V — DESSERT: Choice of ONE Portion of any fruit listed for the Morning Meal or in the additional List of Fruits and Juices prepared with D-Zerta or with plain gelatine.

(C 12, P 3, F 0, Calories 60)

VI — COFFEE, SANKA or TEA: These have no food value. Unless otherwise instructed you may have moderate amounts at any time using no sugar, but saccharin, if necessary, for sweetening.

AVERAGES FOR THIS MEAL: C 62, P 28, F 19, Cal. 531

TABLE X

Page 5 for Diet III

LAMAR DIET PRESCRIPTION NO. III

EVENING MEAL III (To eat from Sundown to Bedtime)

I — SOUP: Made with any fat-free stock (meat, chicken, fish broth or bouillon cube) and vegetables from the Noon Meal in any amount or part of the measured vegetables allowed for this meal ONE CUP.
(C 3, P 4, F 0, Calories 28)

II — ENTREE: (Choice of ONE Portion)

All meats must be free from visible fat and cooked without fat unless specifically allowed (One pat butter equals 1/2 tablespoon fat). No sauces or gravies but vinegar, salt and other condiments may be used moderately. Amounts are roughly the same as 1/4 lb. portions as bought, then trimmed of all fat and inedible parts. Edible portions are about 100 gm:

Beef, boiled, broiled, roast: Two slices 4" x 2" x 1/2" each;
Beef, hamburger, lean: Two patties made from 2" balls;
Beef tenderloin: One broiled steak 4" x 3" x 1";
Chicken, roast, breast: Three slices 3" x 4" x 1/2" each;
Chicken, young, boiled or broiled: One-half, medium size;
Fish, lean, baked, broiled: Two slices 3" x 3" x 1/2" each;
Ham, lean, baked, broiled: Two slices 4" x 3" x 1/4" each;
Lamb chops, lean, broiled: Two, 3" x 2" x 1/2" each;
Lamb leg, roast: Two slices 4" x 2" x 1/2" each;
Liver, broiled: A steak 3" x 5" x 1/2" and 3 strips bacon;
Pork chops, lean, broiled: Two small chops;
Pork leg, roast: One slice 4" x 2" x 1/2";
Turkey breast, roast: Two slices 6" x 3" x 1/2" each;
Turtle: A broiled steak 4" x 3" x 3/4" and 1 pat butter;
Veal chop, broiled: One medium-sized chop;
Veal cutlets, broiled: Two, 4" x 2" x 1/2" each;
Veal roast, cold: Two slices 3" x 2" x 1/2" each;

(C 0, P 20, F 9, Calories 161)

III — VEGETABLES: (Choice of ONE Portion)

Beans, Lima, fresh, frozen or canned: One-third cup;
Beans, Navy and others: One-half cup, boiled;
Beets, boiled: One-half to two-thirds cup;
Carrots, raw or cooked: One-half to two-thirds cup;
Onions, white or yellow: One-half cup;
Parsnips: One-third cup;
Peas, green, canned: One-half cup;
Peas, green, shelled, fresh or frozen: One-third cup;
Potato, baked or boiled: One, size of a large hen egg;
Rice, steamed white: One-third cup;
Rutabagas: One-third to three-quarters cup;
Squash, winter, cooked, fresh or canned: One-half cup;
Turnips, root, white, cooked or raw: 1/2 to 2/3 cup diced;
or TWO generous portions of Noon Meal Vegetables

(C 9, P 1, F 0, Calories 40)

IV — SALAD: Made from TWO generous portions from the Noon Meal Vegetables or from ONE from above list.

(C 9, P 1, F 0, Calories 40)

V — BREAD: Choice of any TWO Portions from the List of Breads, Cereals and Crackers.

(C 26, P 4, F 2, Calories 138)

VI — MILK: Whole milk, one 8-ounce glass

(C 10, P 6, F 8, Calories 136)

VII — DESSERT: Choice of ONE Portion of any fruit listed in the Morning Meal, prepared with D-Zerta or with plain Gelatine.

(C 12, P 3, F 0, Calories 60)

VIII—COFFEE, SANKA or TEA: See "General Instructions"

AVERAGES FOR THIS MEAL: C 69, P 39, F 19, Cal. 603

TABLE XI

Page 3 for Diet IV

LAMAR DIET PRESCRIPTION NO. IV

Average composition of this diet per day: Carbohydrates 192 gm., Proteins 93 gm., Fats 81 gm., Calories 1869.

MORNING MEAL IV (To eat from Awakening to Noon)

I — FRUITS: (Choice of ONE Portion)

Apple, fresh or baked, no sugar: One small (2 1/2")
Applesauce, no sugar: Two-thirds cup;
Banana, peeled: 2/3 of a small one or 1/2 large;
Cantaloupe: 1/2 of a 5" melon or 1/2 cup diced;
Dates, dried: Two, medium sized;
Figs, breakfast type, canned: 1/4 cup scant, no juice;
Fruit cocktail, canned: 1/4 cup scant, no juice;
Grapefruit: One-half large to two-thirds small;
Grapes, green, seedless: One bunch, average 50;
Honeydew melon: One-third of a 5" melon;
Mangoes, Florida: Two-thirds of a small mango;
Olives, green (high in fat content): 4 medium size;

Orange: One, small to medium size;
Papaya, fresh: One small serving (1/2 cup diced);
Peaches, fresh: One, medium large;
Pear, fresh: One, medium small;
Pineapple: One-half to two-thirds cup, diced;
Plums, fresh: Three, medium sized;
Strawberries, fresh: Fifteen large berries;
Tangerines: One large or two small ones;
Watermelon: One cup, cubes or balls, red portion

or JUICES:

Apple juice: One-half cup or four ounces;
Grapefruit juice, unsweetened: Five ounces;
Orange juice, unsweetened: Four ounces (1/2 cup);
Pineapple juice: One-half cup, scant (3 1/2 ounces);
Tomato juice: One full cup or eight ounces
or any ONE Portion from the additional List of Fruits and Juices on back pages of this Diet.

(C 13, P 1, F 0, Calories 56)

II — ENTREE: (Choice of TWO Portions)

Egg, poached, boiled, no fat used in cooking: One.
Bacon, very crisp, all fat drained: Four strips;
Beef, roast, medium fat: One slice 2" x 4" x 1/2";
Cheese, American: One cube 1" x 1" x 1";
Chicken livers: 1/4 cup with 1/2 pat of butter;
Ham, smoked, lean: One slice 2" x 1 1/2" x 1/2";
or any TWO Portions from the List of Additional Substitutions for One Egg on back pages of this Diet.

(C 0, P 12, F 12, Calories 156)

III — BREAD or CEREAL: Two slices, wheat or white, or any TWO Portions from the additional List of Breads, Cereals and Crackers on back pages of this Diet.

(C 26, P 4, F 2, Calories 138)

IV — BUTTER: One pat 1/4" thick from a 1/4 lb. bar or cream, light, one ounce.

(C 0, P 0, F 7, Calories 63)

V — MILK: Whole milk, fresh, pasteurized, homogenized, boiled or made from whole dried milk or from canned evaporated, no sugar added: ONE, 8-ounce glass or measuring cup

(C 10, P 6, F 8, Calories 136)

VI—COFFEE, SANKA or TEA: See "General Instructions"

AVERAGES FOR THIS MEAL: C 49, P 23, F 29, Cal. 549

TABLE XII

Page 4 for Diet IV

LAMAR DIET PRESCRIPTION NO. IV

Noon-Afternoon Meal IV: (To eat from Noon to Sundown)

I — VEGETABLE PLATE: Prepared with any of the following in large, generous amounts, all you wish, raw or steamed, fresh, frozen or waterpack canned vegetables. Lemon or lime juice, vinegar, salt, pepper and other condiments in moderation. No sauces or gravies, but mineral oil dressing may be used if desired:

Asparagus, Bamboo shoots, Beet leaves, Broccoli, Brussels sprouts, Cabbage, Cauliflower, Celery, Chard, Chicory leaves, Cucumbers, Dock, Eggplant, Endive, Fennel, Lettuce, Mushrooms, Mustard greens, Okra, Purslane, Radishes, Rhubarb, Romaine, Sauerkraut, Seakale, Sorrel, Spinach, Summer Squash, Green string beans, Wax string beans, Swiss chard, Tomatoes, Watercress.

Tomato juice, up to 1/2 cup only (4 oz.).

(C 13, P 2, F 0, Calories 60)

II — ENTREE: (Choice of ONE Portion)

American Cheese: One piece 2" x 3" x 1/2";
Brick Cheese, Kraft: 3/16" slice from a 5 pound loaf;
Cottage Cheese, plain: 1/4 cup and one pat butter;
Codfish, boneless, salted: One piece 4" x 2" x 1/2";
Crabmeat, canned or fresh: 1/2 cup and one pat butter;
Eggs: Two, cooked in any way using no extra fat;
Frankfurter: One of average size;
Halibut or any lean fish: Two steaks 3" x 2" x 1/2";
Liver, broiled: 1 slice 4" x 2" x 1/2" and 3 strips bacon;
Lobstermeat, boiled or broiled: 1/2 cup and 1 pat butter;
Oysters, fresh: 1/4 cup (4 to 6) and 1/2 cup whole milk;
Salmon, canned: One-half cup and one-half pat butter;

Shrimp, fresh or canned: 8 large and 1/2 pat butter;
Tunafish, canned, oil drained: One-quarter cup.

(C 1, P 13, F 9, Calories 137)

III — BREAD: Wheat or white, two slices or any TWO Portions from the List of Breads, Cereals and Crackers on back pages of this Diet.

(C 26, P 4, F 2, Calories 138)

IV — BUTTER: One pat 1/4" thick from a 1/4 lb. bar
(C 0, P 0, F 7, Calories 63)

V — MILK: Whole milk, fresh, pasteurized, homogenized, boiled, or made from whole dried milk powder or from canned evaporated, no sugar added: 8 ounces

(C 10, P 6, F 8, Calories 136)

VI — DESSERT: ONE Portion of any fruit listed for the Morning Meal, prepared with D-Zerta or with plain gelatine.

(C 12, P 3, F 0, Calories 60)

VII—COFFEE, SANKA or TEA: See "General Instructions"

AVERAGES FOR THIS MEAL: C 62, P 28, F 26, Cal. 594

TABLE XIII

Page 5 for Diet IV

LAMAR DIET PRESCRIPTION NO. IV

EVENING MEAL IV (To eat from Sundown to Bedtime)

I — SOUP: Made with any fat-free stock (meat, chicken, fish broth or bouillon cube) and vegetables from the Noon Meal in any amount or part of the measured vegetables allowed for this meal ONE CUP.

(C 3, P 4, F 0, Calories 28)

II — ENTREE: (Choice of ONE Portion)

All meats must be free from visible fat and cooked without fat unless specifically allowed (One pat butter equals 1/2 tablespoon fat). No sauces or gravies but vinegar, salt and other condiments may be used moderately. Amounts are roughly the same as 1/4 lb. portions as bought, then trimmed of all fat and inedible parts. Edible portions are about 100 gm.:

Beef, boiled, broiled, roast: Two slices 4" x 2" x 1/2" each;
Beef, hamburger, lean: Two patties made from 2" balls;
Beef tenderloin: One broiled steak 4" x 3" x 1";
Chicken, roast, breast: Three slices 3" x 4" x 1/2" each;
Chicken, young, boiled or broiled: One-half, medium size;
Fish, lean, baked, broiled: Two slices 3" x 3" x 1/2" each;
Ham, lean, baked, broiled: Two slices 4" x 3" x 1/4" each;
Lamb chops, lean, broiled: Two, 3" x 2" x 1/2" each;
Lamb leg, roast: Two slices 4" x 2" x 1/2" each;
Liver, broiled: A steak 3" x 5" x 1/2" and 3 strips bacon;
Pork chops, lean, broiled: Two small chops;
Pork leg, roast: One slice 4" x 2" x 1/2";
Turkey breast, roast: Two slices 6" x 3" x 1/2" each;
Turtle: A broiled steak 4" x 3" x 3/4" and 1 pat butter;
Veal chop, broiled: One medium-sized chop;
Veal cutlets, broiled: Two, 4" x 2" x 1/2" each;
Veal roast, cold: Two slices 3" x 2" x 1/2" each;
(C 0, P 20, F 9, Calories 161)

III — VEGETABLES: (Choice of ONE Portion)

Beans, Lima, fresh, frozen or canned: One-third cup;
Beans, Navy and others: One-half cup, boiled;
Beets, boiled: One-half to two-thirds cup;
Carrots, raw or cooked: One-half to two-thirds cup;
Onions, white or yellow: One-half cup;
Parsnips: One-third cup;
Peas, green, canned: One-half cup;
Peas, green, shelled, fresh or frozen: One-third cup;
Potato, baked or boiled: One, size of a large hen egg;
Rice, steamed white: One-third cup;
Rutabagas: One-third to three-quarters cup;
Squash, winter, cooked, fresh or canned: One-half cup;
Turnips, root, white, cooked or raw: 1/2 to 2/3 cup diced;
or TWO generous portions of Noon Meal Vegetables
(C 9, P 1, F 0, Calories 40)

IV — SALAD: Made from TWO generous portions from the Noon Meal Vegetables or from ONE from above list.
(C 9, P 1, F 0, Calories 40)

V — BUTTER: One pat 1/4" thick from a 1/4 lb. bar, or Salad Oil Dressing, two-thirds tablespoon.

(C 0 P 0, F 7, Calories 63)

VI — BREAD: Choice of any TWO Portions from the List of Breads, Cereals and Crackers.

(C 26, P 4, F 2, Calories 138)

VII — MILK: Whole milk, one 8-ounce glass

(C 10, P 6, F 0, Calories 136)

VIII — DESSERT: Choice of any TWO Portions from the List of Fruits and Juices, prepared with ONE Portion of D-Zerta or plain gelatine.

(C 21, P 6, F 0, Calories 120)

IX — COFFEE, SANKA or TEA: See "General Instructions"

AVERAGES FOR THIS MEAL: C 81, P 42, F 26, Cal. 726

TABLE XIV

Page 2 for All Diets

LAMAR DIET PRESCRIPTION

GENERAL INSTRUCTIONS

This diet Prescription shows, in the form of simple menus, the exact amounts and kinds of foods you must eat.

There is nothing left for you to figure out as everything has already been calculated so that you will get the proper amounts of Carbohydrates (C), Proteins (P), and Fats (F), as well as all the Calories, Vitamins and Minerals that you need daily.

Read your menu and select your food from the successive lists of items and measure your portions carefully. A measuring cup, measuring spoons and a six-inch washable plastic ruler are all the equipment you need.

If you like a snack between meals you may have it by reserving some food from the previous meal. Many people do feel better when they eat often. For that reason your meals are listed for Morning, Noon-Afternoon and Evening and you do not have to eat each one of them all at once. A part of your Morning Meal may be had for breakfast and the remainder eaten as a mid-morning lunch. The same may apply to the other two meal-lists. If your diet includes a Bedtime Meal, be sure that you eat that too each night.

Only items of food listed are to be eaten or drunk. If you think about eating or drinking anything, see whether it is listed here. If it is not listed: DO NOT TAKE IT! If it is listed, see then HOW MUCH exactly you are allowed and have just that amount, NO MORE!

DO NOT SKIP ANY ITEM OF FOOD! This prescription is well balanced to cover your needs but if you skip or measure wrong, the proper balance will be broken and the diet may then do you harm instead of the good intended.

Additional Lists of Portions, figured to have the same average food values as those in the regular menus, are included in order to increase the variety of your choices.

Unless you are otherwise instructed, use salt with great caution: very little in cooking and none at the table. Other condiments and spices may be used with moderation. Avoid fried foods unless your diet specifically allows enough butter or other fats to use for frying. Use no sauces or gravies of any kind.

Unless you are allowed butter or salad oil, use only mineral oil dressings for your salads:

MINERAL OIL MAYONNAISE: Yolk of one egg; 1 to 3 cups mineral oil; 1 to 2 tablespoons vinegar; salt; paprika; mustard, to taste. Beat yolk thoroughly; add mineral oil drop by drop while constantly beating until all of it is well worked in. Beat in the other ingredients, the vinegar particularly, very slowly to get the right consistency and flavor. Additional variations may be created by the use of small portions of mashed garlic, horseradish, chopped sour or dill pickle, or tomato paste softened in vinegar.

MINERAL OIL FRENCH DRESSING: Mix well in a bottle one-half cup mineral oil and two-thirds cup vinegar. Add one-fourth grain saccharine, salt, pepper and cayenne to taste and enough paprika to color. Shake well before using.

Two to three dessertspoons of these recipes have no practical food values, but remember that they are mildly laxative if used in excess.

Pleasing desserts may be made with your allowance of fruit and with D-Zerta, a chemically sweetened form of Jell-O made without sugar, or with plain gelatine, like Knox's, sweetened with saccharin. Two to three regular portions of D-Zerta or of plain gelatine are allowed daily.

to be used either as dessert, with fruit or plain, or as salads, aspies, with your allowed vegetables.

Stiff-beaten egg-white meringue, sweetened with saccharin and flavored with lemon or vanilla extracts and softened with skim milk may be used to top your desserts.

COFFEE, SANKA, KAFFEE-HAG and TEA have no food value and unless otherwise instructed you may use moderate amounts at any time provided you use no sugar, cream or milk except from your allowance. Sweetening with saccharine is permissible. Remember that saccharine, if placed in very hot drinks, may turn rather bitter. A pleasant drink is "Half-and-Half," made with hot milk (whole or skim, according to your diet-prescription), and strong coffee sweetened with saccharin.

TABLE XV

Page 6 for All Diets

ADDITIONAL LIST OF PORTIONS: FRUITS, JUICES

AVERAGE COMPOSITION PER PORTION:

RANGE: Carbohydr., 12-14 gm.; Cal. 50-65 gm. per portion

FRUITS:; (Fresh or canned in water or juice; no sugar added, unless otherwise specified)

Apricots, canned in syrup: Six halves, no syrup.

Apricots, canned, waterpack: 9 halves, with 4 table-
spoons juice.

Apricots, dried: Three halves.

Avocado (adds 4 gms. of fat): One-quarter of a 4" pear.

Blackberries, fresh or waterpack canned: Two-thirds cup.

Blueberries, fresh or waterpack canned: Two-thirds cup.

Cherries, canned, juice pack (no sugar): One-half cup,
red or white.

Cherries, fresh, sour: One-half cup, pitted.

Cherries, fresh, sweet: 15-20 small, 10-12 large.

Cranberries, fresh: Two-thirds to one cup.

Cranberry jelly: One tablespoon, level.

Cranberry sauce: One tablespoonful, heaping.

Currants, fresh all: Three-quarter cup, scant.

Figs, dried: One medium-sized.

Figs, fresh: One large or two very small size.

Gooseberries, fresh: One cup.

Grapefruit, canned in syrup: One-quarter cup, scant.

Grapes, American: Eighteen to twenty grapes.

Grapes, green, seedless: One bunch (average fifty).

Grapes, Malaga or Tokay: Sixteen to eighteen.

Guavas, fresh: One medium-large.

Kumquats, fresh: Five, medium size.

Lemon, fresh: One and one-half, medium size.

Lime, fresh: One, large-sized.

Loganberries, canned, juice pack: One-half cup.

Loganberries, fresh: Two-thirds to three-quarter cup.

Mulberries: Two-thirds cup, scant.

Nectarines: Two small or one large.

Olives, ripe: Six to seven small (high fat).

Peaches, canned: 3 1/2 halves with 2 tablespoons juice.

Pears, canned: Three halves, 1 1/2 tablespoon juice.

Plums, canned: Four medium, 2 tablespoons juice.

Prunes, strained, Gerber's: 1/2 to 1/3 cup, scant.

Pumpkin, canned: Two-thirds cup.

Raspberries, canned, juice pack: One-half cup.

FRUIT JUICES: (Unsweetened, unless otherwise specified)

Apricot juice: One-half cup (4 oz.).

Grape juice, bottled: Two and two-thirds ounces.

Grapefruit juice, canned, sweetened: Three ounces.

Grapefruit juice, canned, unsweetened: Five ounces.

Lemon juice, fresh: Five ounces (10 tablespoons).

Lime juice, fresh: Five ounces (10 tablespoons).

Orange juice, canned: One-half cup, scant (3 1/2 oz.).

Orange & Grapefruit juice, canned: 3 1/2 ounces.

Papaya juice, canned: One-half cup, scant (3 1/2 oz.).

Prune juice: Two ounces (1/4 cup).

TABLE XVI

Page 7 for All Diets

ADDITIONAL LIST OF PORTIONS: SUBSTITUTIONS FOR ONE EGG

AVERAGE COMPOSITION PER PORTION:

C 0. P 6, F 6, Calories 78

EGG: One, medium size, raw, poached, boiled or scrambled with two tablespoons of your milk allowance in the top of a double boiler. (If butter is allowed in this meal you may use it in cooking your egg in any other way you please).

Bacon: Four strips, very crisp.

Beef, roast, medium fat: 1 slice 3" x 4" x 1/2".

Beefsteak, loin, medium fat: 1 slice 2" x 2" x 1/2".

Beefsteak, round, lean: 1 slice 4" x 1" x 1/2" with one
teaspoon cooking fat or butter.

Cheese, American: One cube 1" x 1" x 1".

Cheese, cottage: 1 heaping tablespoon or 2 level table-
spoons using also 1 tablespoon heavy cream or 1 pat butter.

Chicken: One slice 4" x 1" x 1/2".

Chicken livers: One-quarter cup and 1/2 pat butter.

Codfish ball: Oneball (1 1/2" diameter) fried with two-
thirds pat butter.

Fish, lean: 1 slice 3" x 3" x 1/2" with 1 pat butter (1/4").

Frankfurter: 3/4 of average-sized one.

Ham, smoked, lean: One slice 2" x 1 1/2" x 1/2".

Heart, beef: One slice 2" x 2" x 1/2".

Lamb chops: One small chop.

Lamb, roast leg: One slice 1" x 2 1/2" x 1/2".

Liver, Calf: One slice 1" x 1" x 1/2" with 3 strips bacon.

Pork chop, lean: One, medium sized.

Salmon, canned: 1/6 cup with 1/2 pat butter.

Sardines, canned: One large to three small.

Sweetbreads: One, average size.

Turkey, medium fat: One slice 6" x 3" x 1/2".

TABLE XVII

Page 8 for All Diets except Diet 1

ADDITIONAL LIST OF PORTIONS:

BREADS, CEREALS, CRACKERS

AVERAGE COMPOSITION PER PORTION:

C 13, P 2, F 1, Calories 69

(Portions in this list are freely interchangeable as they
have been arranged to practically identical values; one
portion of bread equals one portion of cereal equals
one portion of crackers.)

BREADS: Bran; Gluten; Graham; Raisin; Rye, dark;
Wheat, cracked; OR Wheat, white: One average slice.

Wheat, enriched: White, with soya; OR Whole Wheat:
One thin slice.

Biscuit, baking powder: 1 1/2 biscuits, 2" diameter.

Boston Brown Bread: One slice, 3" x 1/2".

Corn Bread: One piece, 1" x 2" x 1".

French or Vienna: One slice, 1" thick.

CEREALS: Barley, pearled, pot; Barley, whole OR Bran
(Kellogg's All Bran): One-third cup, cooked.

Corn meal; Cream of Wheat; Farina; Hominy or Grits;
Macaroni, plain; Noodles, egg; Pettifohn's; Ralston, Instant
Wheat; Ralston, Wheat Cereal; Rice, brown; Rice, wild or
white; Spaghetti, plain OR Wheatena: One-half cup, cooked.

Oats, rolled; Pabena; Pabulum OR Wheat, cracked: One-
third to one-half cup.

Cheerioats; Grapenut flakes; Hominy, canned; Krumbles;
OR Post Toasties: One-half cup.

Corn, popped, no fat; Sparkies, Wheat; OR Sparkies,
Rice: One cup.

Muffets: One biscuit.

Krispies, Rice: OR Pep, Kellogg's: 1/2 to 2/3 cup.

Bran Flakes: One-quarter cup.

Corn Flakes: Two-thirds cup.

Gerber's Dry Cereal: 7 tablespoons, level, dry.

Gerber's Dry Oatmeal: 8 tablespoons, level, dry.

Grapenuts: One tablespoon, heaping.

CRACKERS: Arrowroot, N. B. Co.: Three biscuits.

Cheese Crackers: Three crackers (2" diameter).

Crackers, Oyster: Twelve pieces.

Crackers, Ritz: Four pieces.

Crackers, Soda (2 1/2" x 2 3/4"): Two crackers.

Crackers, Saltines: Four crackers (2" squares).

Crackers, Water: Two crackers.

Crackers, Whole-Wheat, N. B. Co.: Two crackers.

Holland Rusk (30 to 1 lb.): One piece.

Matzoth Wafers: One piece (6" diameter).

Pretzel, medium: One piece (24 to 1 lb.).

Pretzel sticks (3"): Five to six sticks.

Rykrisp (7/8" x 3" x 5/8"): Three pieces.

Triscuit (2" squares — 55 to 1 lb.): 2 1/2 pieces.

Zweiback (60 to 1 lb.): Two pieces.

TABLE XVIII

Page 5' for PZI cases

BED-TIME MEAL

Choice of any ONE of the following combinations:

I

Milk (whole): One cup or glass (8 ounces).
Bread, plain or toasted: One slice.
Butter: One pat 1/4" thick from a 1/4 pound stick.

II

Milk (whole): One cup or glass (8 ounces).
Cream (light or "coffee"): Two tablespoons (1 ounce).
Cereal: One portion (see List).

III

Banana, sliced: One-half, medium large, or any one
Fruit Portion from the list.
Milk (whole): 3/4 cup (six ounces).
Cream, heavy (40%): 1/4 cup (2 oz.), or light cream:
1/2 cup (4 oz.).

IV

One fried (grilled) Hamburger on a bun.
A small glass of orange juice (4 ounces).

V

A grilled or plain cheese sandwich (buttered).
A cup of Tea or Coffee with cream.

AVERAGES FOR THIS MEAL: C 25, P8, F 16, Calories 276

(Averages are to be added to Diet's Daily Totals)

SUMMARY

The existing need for simplification in the methods for the calculation and the instruction of diet prescriptions for diabetic patients may be fulfilled by the use of a system of diet prescriptions arranged by the author, in which all calculations have already been made beforehand.

The physician is given a wide choice of basic formulae to select the one most suited to his patient's needs or to modify as warranted through the simplest of additions or by crossing off the undesired items.

The patient is given a complete set of simple instructions, menus for each meal with a very wide choice of variations and portions easily measured without the need for scales or any calculation whatsoever.

Although primarily devised for use with clinic patients where personnel trained for patient-instruction is limited or not available, these diet-prescriptions have also been exceedingly successful in the handling of private diabetic patients.

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Etiology of Prolapsed Gastric Mucosa: with an Illustrative Case Report

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IN A PREVIOUS ARTICLE, the following theory was offered as a possible etiological factor for the production of prolapse of redundant or hypertrophied gastric mucosa: "A benign peptic ulceration located at the base of the duodenal bulb or in the prepyloric area may, in the process of healing, produce a local gastritis. This inflammation may lead to a localized

hypertrophy of the gastric rugae of the pre-pyloric area which eventually may prolapse through the pylorus into the base of the bulb at a time when no other sign of the original ulcer may be present anymore" (1).

This belief was only considered a clinical possibility which gained credence only with Melamed and Hiller's (2) reported case of ulceration in an area of prolapsed mucosa. Since then, another case has been

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tion, who assumes no responsibility for the opinions expressed or conclusions drawn by the authors.

We are indebted to Dr. S. Osher for bringing this case to our attention.

We are further indebted to Dr. H. Necheles, Director of the Department of Gastro-Intestinal Research, Research Institute, Michael Reese Hospital, who first brought this etiological possibility to our attention in an oral communication some time previously.

Submitted May 15, 1947.

TABLE I

No. & Date of Admission	Presenting Complaints	X-Ray Findings	Other Positive Findings	Condition on Discharge
1. 7/10/40	Stomach trouble since September, 1939, passed several tarry stools. Epigastric pain beginning in June 1940. Pain relieved by food and soda bicarb. Bilateral indirect hernias.	Deformed bulb suggestive of duodenal ulcer (x-rays not available).	Gastric analysis: Fast-ing: Free: 46°; Total: 60°	Good response to Sippy regime. Herniorrhaphy.
2. 12/5/41	Recurrence of epigastric pain and tarry stools.	Slight sacculatation of posterior border of bulb. Impression duodenal ulcer (no film).	Stools: 4+ occult blood. Gastric analysis: Free: 40°; Total: 52°.	Good response to Sippy regime.
3. 9/16/42	Recurrence of hernia with vague pain in epigastrium.	Constant niche on greater curvature of pyloric anterior border of bulb. Impression prepyloric ulcer (fig. 1).	Gastric analysis: Free: 60°; Total 74°.	Asymptomatic after herniorrhaphy and Sippy regime.
4. 9/17/43	Pains across abdomen for two weeks, tarry stools on three occasions.	Slight sacculatation of inferior border of bulb. Impression: Residuals of an old duodenal ulcer (fig. 2)	Stools negative for occult blood.	Good response to Sippy regime.
5. 7/16/45	Recurrence of "gas pains" with bloating 1-2 hours after meals. Occasional tarry stools for 1 month.	Duodenal bulb spastic with inconstant mural irregular hyperperistalsis in stomach. Impression: probably duodenal ulcer and diverticulosis coli (fig. 3).	Stools showed 4+ occult blood on three occasions.	Good response to amphogel.
6. 10/1/45	Recurrence of pain, following dietary indiscretion. 1 or 2 tarry stools.	No intrinsic pathology in stomach or duodenum. (fig. 4).	Gastric analysis: Fast-ing: Free: 30°; Total 42°	Good response to medical management.
7. 11/1/46	Epigastric pains 3 weeks 1-2 hours p.c. and at 1-3 a. m.	Impression: hypertrophic gastritis. On review, a constant crater-like projection on lesser curvature of prepyloric area, suggestive of pre-pyloric ulcer (fig. 5). Repeat x-rays 1 month later: no organic disease of stomach or bulb. Slight hyperplasia of the mucosa at the antral segment (fig. 6).	Gastric analysis: Fast-ing: Free: 44°; Total 88° Gastroscopy revealed superficial gastritis of the antrum of the stomach and probable benign gastric pre-pyloric ulcer on lesser curvature.	Good response to medical management.
8. 6/9/47	Epigastric pain — 2 mos. Pain in right upper quadrant, 1 mo. Minor episodes of hematemesis and melena, 1 month.	Two upper gastro-intestinal x-rays reported as normal, but on review, in the first series, the pre-pyloric area seemed irregular, no definite niche being seen, but base of duodenal bulb had cauliflower deformity characteristic of a prolapse. Impression: antral gastritis with severe prolapse (fig. 7). Two weeks later, x-ray revealed a normal stomach and duodenum.	Gastric analysis: Fast-ing: Free: 16°; Total 32°	Patient free of epigastric pain but still has occasional slight epigastric fullness with eructation.

found which may shed considerable light on the cause of this disease, because it illustrates an etiological sequence quite clearly early.

CASE REPORT:

A 57 year old white male has had seven previous admissions to Hines Hospital, which are summarized in Table 1. He had been treated for a duodenal ulcer which apparently had healed prior to his last hospitalization in 1946 at which time he was told that he had a pre-pyloric ulcer.

Following his last discharge, the patient remained relatively asymptomatic until recently. On 6-9-47 he was re-admitted to Hines Hospital with complaints of epigastric pain similar to that suffered previously. This consisted of diffuse cramping pain across the upper abdomen,

especially on the right side, together with epigastric distention. It usually occurred immediately following the noon or evening meal and bore no constant relationship to food intake, but was aggravated by certain types of food. He had frequent nausea and occasional vomiting with the pain. On one occasion, following a bout of prolonged vomiting, he had brought up a half cupful of fresh blood. He also stated that he had frequent tarry stools during the past month. For one month prior to admission the patient had noted an additional and entirely new pain in the right upper quadrant appearing from half to one hour after meals, associated with the occurrence of gas in the stomach. This pain was relieved only partially by amphogel. It was described as a sensation of pressure in the right upper quadrant lasting from fifteen minutes to one-half hour, occurring irregularly during the month with about eight episodes in all. He had not lost

weight or strength and his appetite remained fairly good, but he stated that he felt rather weak for a day or two prior to admission and this coincided with hematemesis and melena. At the time of admission, he was having irregular pains frequently during the day and was awakened several times during the night.

On physical examination, there was only diffuse tenderness throughout the epigastrium and the right upper quadrant. Two separate points of maximum tenderness were found. The first was about one inch above and to the right of the umbilicus, and the other at the medial border of the right costal margin. There were old scars from a bilateral inguinal herniorrhaphy. The examination was otherwise negative except for the presence of slight prostatic enlargement. The patient stated that he could not tolerate milk.

Following his admission, the epigastric pain subsided in a few days. However, the patient continued to complain at intervals of localized pain in the right upper quadrant. Repeated physical examinations failed to demonstrate any further abnormalities, although it was felt at one time that the liver edge was palpable several fingers down on inspiration. The patient noted that he would obtain relief of the pain in the right upper quadrant by moving about or changing his position. A special effort was made to determine the presence of a diaphragmatic hernia, but this was not demonstrable by x-ray.

The following laboratory data were obtained: blood count and urine were normal. Fasting gastric free and total acidity were 16° and 32° respectively. Serology, total proteins, icteric index, serum bilirubin, B.S.P. and cephalin flocculation tests, were all within normal limits. A barium enema confirmed diverticulosis of the colon which had been noted on his previous admission. A gallbladder film on 6/17/47 showed only fair visualization of the gallbladder, but on 7/7 there was good visualization.

The patient had been gastroscopied on his previous admission, and a diagnosis of superficial antral gastritis and a probable prepyloric ulcer was made. X-ray pictures at

that time showed a marked irregularity and a questionable niche on the lesser curvature of the pre-pyloric area which was interpreted as prepyloric ulcer. Two gastro-intestinal x-ray series were done during his present hospital stay and both were reported as normal. On reviewing these latest films, however, the prepyloric area still appeared irregular, no definite niche being seen, but the base of the bulb showed a cauliflower-like deformity which is characteristic of a moderately severe prolapse. The appearance of the prepyloric area was consistent with an antral gastritis. A second gastroscopy was advised, but was refused by the patient. Because of the slight irregularity of the prepyloric area the possibility of a sclerous carcinoma could not be eliminated definitely, but this was rather improbable in view of the patient's course and response to ulcer management.

It was felt that the symptoms are best explained on the basis of a recurrence of a local superficial gastritis and prolapse. It was also interesting to note that at the time of the patient's freedom from symptoms a repeat upper gastro-intestinal x-ray failed to show the prolapse as seen two weeks previously. The patient, at this time, presented insufficient evidence to warrant a diagnosis of recurrent or persistent prepyloric ulcer.

On reviewing the history and the course of events in this case, we feel that the patient has been having some epigastric distress for many years before his initial complaint in 1939. In 1940, an x-ray diagnosis of duodenal ulcer was made; unfortunately these films were not available for evaluation, but the roentgenologist reported a markedly deformed bulb. This was also the impression on re-examination five months later, when he had a recurrence of symptoms. The following year, a constant niche was described on the greater curvature of the pyloric antrum (Fig. 1), but in 1943 the impression was that of a deformed bulb due to residuals of an old duodenal ulcer (Fig. 2). The patient was asymptomatic until July 1945, when the x-ray report was that of a spastic bulb with inconstant mural irregularities, probably duodenal ul-

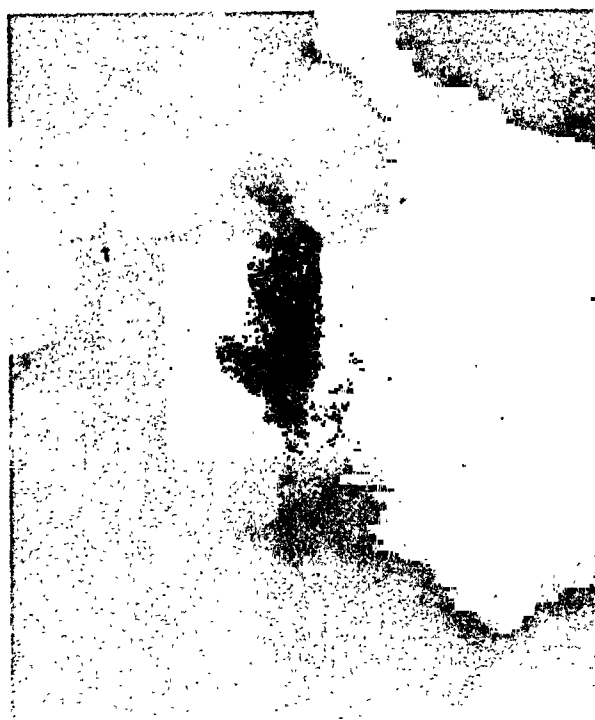


Figure No. 1 — Third admission, 9/18/1942. A constant niche was seen on the greater curvature of the pyloric antrum, and the impression was of a prepyloric ulcer, probably benign.

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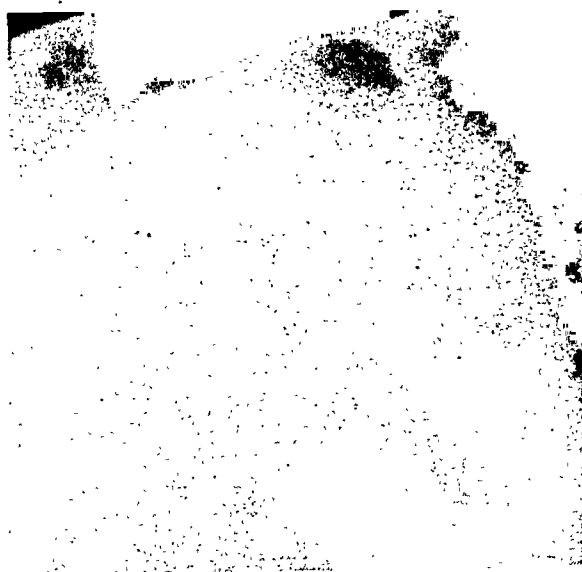


Figure No. 2 — Fourth admission, 9/17/1943. On fluoroscopy as well as roentgenography a slight degree of sacculations was noted on the inferior border of the duodenal bulb, which was considered as residual of an old duodenal ulcer.

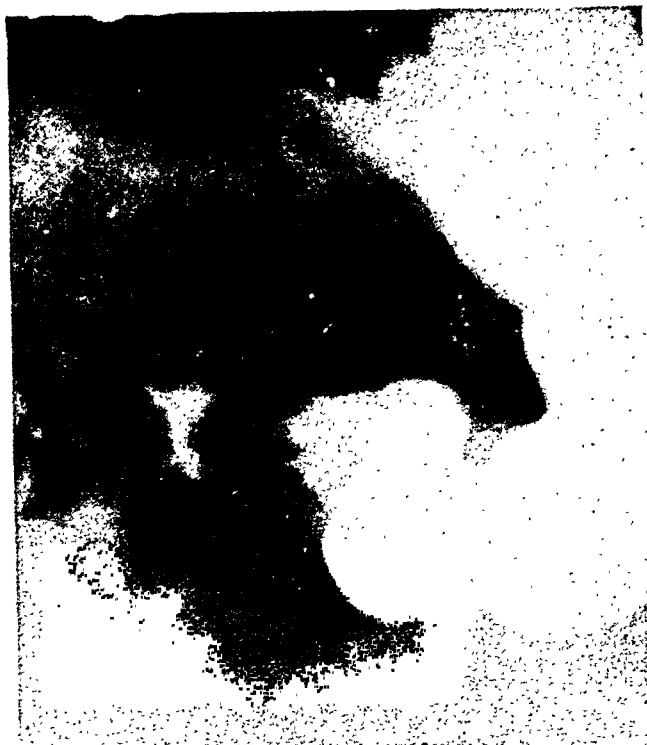


Figure No. 3 — Fifth admission, 7/24/1945. The duodenal bulb appeared spastic with inconstant mural irregularities, and hyperperistalsis was noted fluoroscopically. Diagnosis of probable duodenal ulcer. Diverticulosis of the colon was also noted at this time.

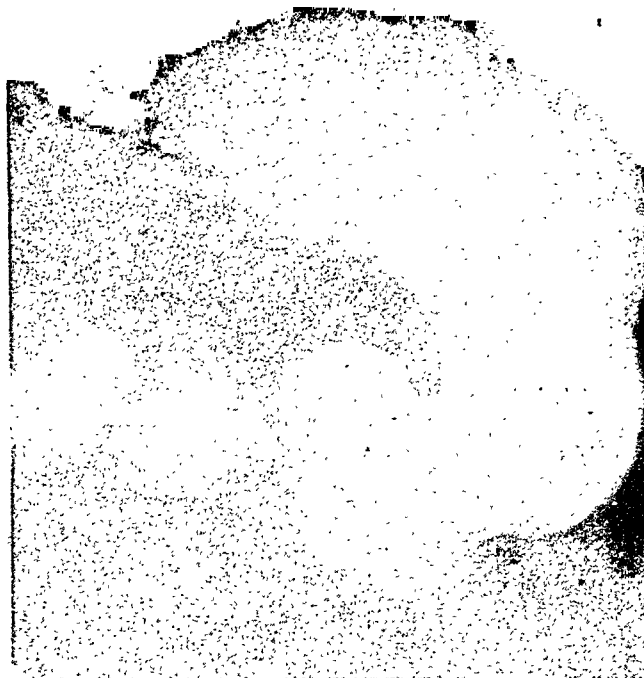


Figure No. 5 — Seventh admission, 11/4/1946. A hyper-trophic gastritis was diagnosed, but on review a constant crater-like projection on the lesser curvature of the prepyloric area suggestive of a prepyloric ulcer was noted.

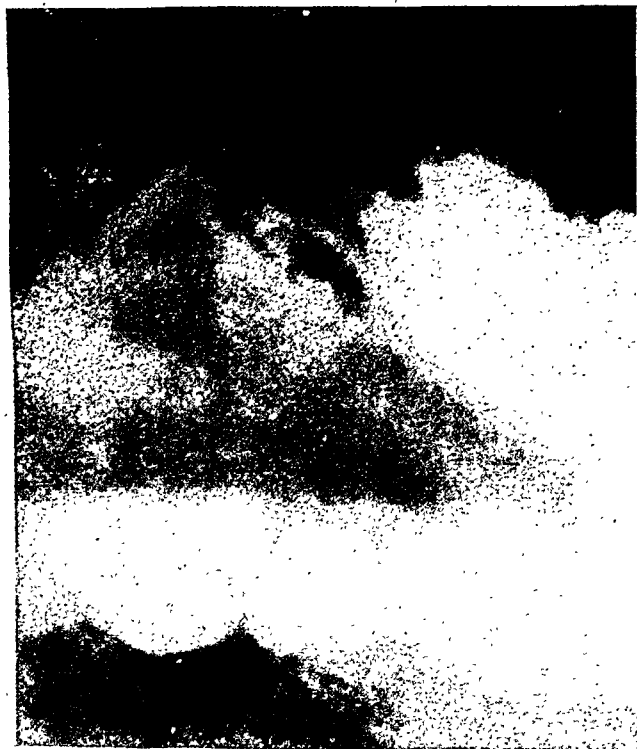


Figure No. 4 — Sixth admission, 10/1/1945. Diagnosis of a perfectly normal stomach and duodenum, although patient complained of recurrence of pain as well as several tarry stools.

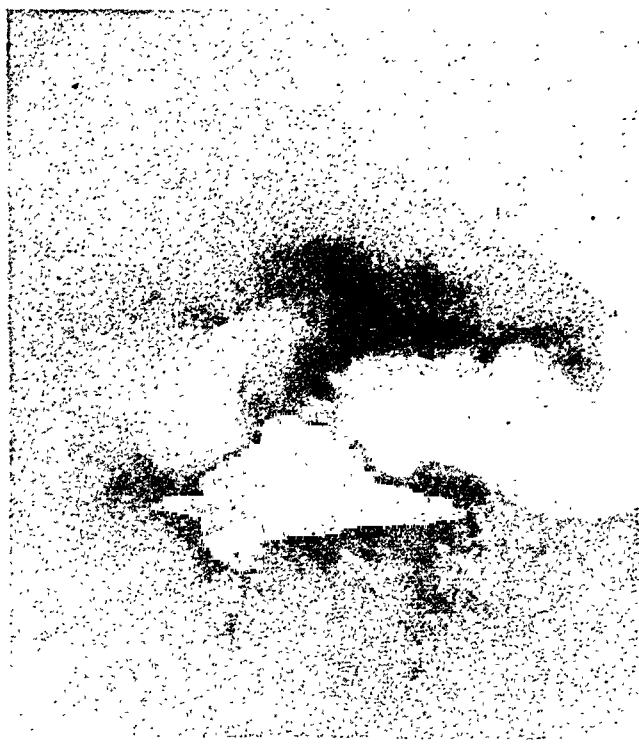


Figure No. 6 — One month later, 12/4/1946, repeat x-rays did not show the prepyloric ulcer but an antral gastritis. However, a gastroscopy done at this time revealed a superficial antral gastritis and a probable benign gastric prepyloric ulcer.



Figure No. 7 — Last admission, 7/19/1947. Characteristic cauliflower-like deformity at the base of the duodenal bulb, which fits the roentgenographic description of a moderately severe prolapse of the gastric mucosa.

cer (Fig 3). During an admission in October 1945, the roentgenologist reported no intrinsic pathology of the stomach or duodenum (Fig 4). The following year, a diagnosis of hypertrophic gastritis was made on the basis of the x-ray film shown in Figure 5, but on review of the film a crater-like projection on the lesser curvature of the prepyloric area suggestive of a prepyloric ulcer was noted. Gastroscopy revealed a superficial gastritis of the antrum of the stomach and a probably benign gastric prepyloric ulcer on the lesser curvature, which was difficult to bring into view because of the overhanging angulus. Repeat x-rays (Fig 6) one month later were consistent with antral gastritis, but no ulcer niche or crater could be made out. The plates of the present admission fail to show the prepyloric ulcer, but they do show the hypertrophic rugal pattern of the antrum besides a relatively severe degree of prolapsed gastric mucosa (Fig 7). Following medical management for two weeks, the prolapse had been reduced and the patient was free of epigastric pain, but still had occasional sense of fullness with eructations. The x-rays still showed some antral gastritis and in Figure 8 a normal duodenal bulb is seen.

This sequence of ulcer, gastritis, hypertrophied folds, prolapse, would also tend to explain a case reported from the Mayo Clinic (4) of a patient with chronic hypertrophic gastritis complicated by pyloric obstruction. Following surgery, the pathologist noted that a prolapsed portion of the mucosa formed an almost occluding diaphragm. The lumen at that point would scarcely admit the tip of a lead pencil. After the specimen was opened, a diagnosis of erosive gastritis was made. Although no mention was made in the case report of an ulcer at the time of surgery, his long history of epigastric distress would fit in with the thought of an original ulcer which produced a gastritis, hypertrophic folds, and later, a prolapse.

Appleby's attempt to rationalize the presence of occult blood in the stools of four of his seven cases follows the same line of reasoning. He states "the blood . . . is

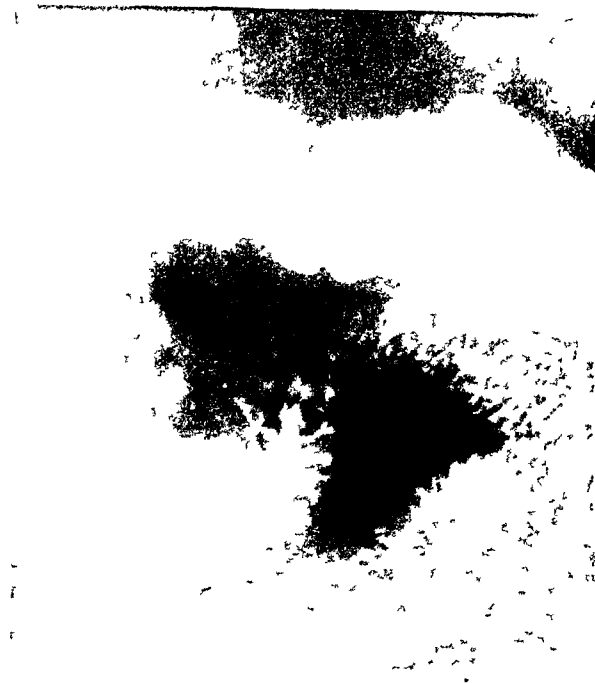


Figure No. 8 — After medical management and bed rest of two weeks duration. Normal stomach and bulb. The ease of reduction of prolapse is a typical feature of this condition, and aids in explaining why many of these cases are not discovered by x-ray.

probably from small cracks or ulcers on the surface of the prolapsed turgid mucosa."

The symptoms of our patient would for the most part fit with the complex described by Appleby (3). His seven cases of prolapse proven by partial gastrectomy, all complained of intermittent cramping pain, aggravated by food and usually relieved by emesis. There may be an associated weight loss, secondary anemia, high total acidity, retention with a low free acidity, and no evidence of malignancy. In our patient, the alleviation of pain with change of position may be a characteristic of prolapse.

The easy reduction in our case of the prolapse under medical management would seem to contradict the advisability of surgery unless definite obstruction, intractable to conservative regime, is present. The surgical procedure should then be up to the surgeon, as even a partial gastrectomy in good hands has a low mortality, today. We do not feel, as does Appleby, that less radical surgical procedures will in most instances prove to be inadequate.

SUMMARY

The sequence of benign peptic ulceration followed by gastritis which, on healing, produces hypertrophic gastric rugae and later a prolapse of gastric mucosa into the duodenal bulb has gained credence as the possible etiological mechanism in this presented case. It is possible that this mechanism plays a more general role in the causation of prolapse. An attempt is made to explain the findings of two other observers who have recently reported on prolapse of the gastric mucosa on the same basis.

It is our belief that surgery should be restricted to cases with intractable pyloric obstruction.

September 29, 1947.

ADDENDUM

Since the time this original case was sent to the publishers, two more patients showing the possible sequence of ulcer-gastritis-prolapse were admitted to the Veterans Administration Hospital, Hines, Illinois. Furthermore, the sequence of peptic ulcer followed by a hypertrophic gastritis is seen in the recent case report of Banks et al (5).

The two cases most recently seen are briefly outlined:

CASE ONE:

A 55 year old white male who in 1941 began to have severe pain in stomach which went away when patient would lie on stomach. Had recurrent attacks in 1944 and 1945 when definite x-ray evidence of duodenal ulcer was found. This pain would be most severe at night and only occasionally relieved by vomiting, amphetel or soda. Last admission was in July, 1947, and patient stated that pres-

ent attack was the worse, so far, with almost constant pain. This time, x-ray revealed a moderate prolapse of gastric mucosa with no evidence of duodenal ulcer.

CASE TWO:

This 54 year old white male was last admitted to this hospital in June, 1945, after an episode of hematemesis and melena. X-rays at that time revealed a duodenal ulcer. Following his discharge he followed his diet and had no pain. Six months prior to this admission in July, 1947, he stopped his diet, drank alcohol heavily, smoked considerably, and drank large quantities of coffee. His symptoms recurred and were mainly of pain an hour after meals, beginning as a gnawing sensation to the right of the umbilicus followed by a steady aching pain in the epigastrium. He obtained relief from baking soda in 10 to 15 minutes. This was also associated with recurrent attacks of vomiting. The Gastro-Intestinal x-rays on this admission showed slight redundancy of the hyper-plastic gastric mucosa in the pyloric segment with partial prolapse into the base of the duodenal bulb. No ulcer could be demonstrated.

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Abstracts Of Current Literature

CLINICAL MEDICINE

Mouth and Esophagus

JOANNIDES, M. AND LITSCHGI, J.: *Diagnostic problems in surgical diseases of the esophagus.* (Med. Times, 75, 7, July 1947, 179-184).

These authors have obtained no relief of cardiospasm by means of vagotomy, and advise surgical repair of the cardiospasm. Interestingly, they believe that hiccup is the result of clonic spasm of the esophagus and bears no relation to the diaphragm.

Stomach

BARSH, A. G.: *Diverticula of the duodenum.* (Texas State Jour. Med., XLIII, I, May 1947, 21-23).

The incidence of duodenal diverticula by x-ray examination in a series of 2100 consecutive cases was 1.5 per cent. The incidence of 216 autopsies was 5 per cent. Reports seldom show an incidence of over 3 per cent by radiographic diagnosis. The highest incidence is from 50 to 70 years of age. The cause is unknown. Diagnosis can only be made by careful x-ray examination. Some authorities believe that duodenal diverticula do not produce symptoms. If medical treatment is employed, the ulcer regimen serves the purpose well. Surgical extirpation is indicated in cases where upper abdominal pain or vomiting cannot otherwise be explained, where inflammation in the pouch exists or where a calculus has become lodged in the diverticulum.

BARNETT, T. N.: *Early diagnosis and treatment of acute peptic ulcer.* (Southern Med. J., 109, 5, May 1947, 144-146).

By treating acute peptic ulcers strenuously by bed rest and alkalinization, the author believes the profession is making its most successful type of attack on chronic ulcer. Before a crater has formed, the roentgen manifestations of acute ulcer are pylorospasm and duodenal spasm (the so-called "pseudo-ulcer") and these signs, associated with epigastric distress in a male patient, are almost enough to make the diagnosis of acute ulcer. The ambulatory treatment is not satisfactory.

WOLF, S. AND WOLFF, H. G.: *An experimental study of changes in gastric function in response to varying life experiences.* (Rev. Gastroenterology, June 1947, 14, 6, 419-425).

By observation of gastric mucosa, gastric motility and gastric acidity by suitable methods as continually applied to a patient with a permanent gastrostomy opening, the authors are able to correlate changes in gastric activity with changes in the life experiences of the patient. Gastric hyperacidity was associated with heartburn and epigastric gnawing sensation. Gastric hypoacidity was accompanied by feelings of fullness and by nausea. Anger and preparation to meet an aggravating situation calls forth gastric hyperactivity but a feeling of defeat is associated with gastric hypoactivity and nausea.

FORSSELL, P.: *Gastroduodenal ulcers in children of school age.* (Nordisk Med., May 16, 1947, 20, 34, 1162-1165).

Seven children, aged 9 to 14, with chronic abdominal disturbances were found by x-ray examination to be suffering from peptic ulcers. In one case, a boy of 12, there was a gastric ulcer while the other patients, four boys and two girls, were afflicted with duodenal ulcers. Peptic ulcers in children are not uncommon, the symptoms being similar to those in ulcer of adults. A detailed history and radiographic examination of children with indigestion facilitate early diagnosis.

JUDD, E. S. JR. AND MOE, A. E.: *Chronic hypertrophic gastritis complicated by obstruction.* (Proc. Staff Meet. of the Mayo Clinic, Vol. 22, No. 12, June 11, 1947).

The case is presented of a man of 53 who complained of vomiting in the morning foods eaten the previous evening but in whom x-ray examination revealed no ulcer or evidence of other pathological condition of the stomach or duodenum. He improved to some extent on a bland diet but after a few years the vomiting became worse, associated with weight loss. Although again the examinations were negative except for gastric retention of food, because of a persistent achlorhydria operation was undertaken and a greatly distended stomach was found. A resection of 12 cm. of the stomach and 2 cm. of the duodenum was done, and the specimen revealed no ulcer or cancer but a chronic hypertrophic gastritis, some of the mucosal folds having caused pyloric block. His recovery and subsequent course were uneventful.

LANDAU, A.: *Intravenous atropine for peptic ulcer.* (Brit. Med. Journal, June 28, 1947, p. 928).

The author presents a case in which a gastric ulcer was radiologically and clinically cured in a very short time by a form of treatment involving cod liver oil before breakfast and the daily intravenous injection of atropine sulfate, gr. 1/60 dissolved in 10 cc. of 10 per cent calcium gluconate. This is characteristic of this physician's standard treatment for peptic ulcer.

ALMQUIST, G. O.: *Leiomyoma of the stomach.* (J. Indiana State Med. Assoc., 40, 7, July 1947, 646-649).

In the case of leiomyoma of the stomach presented by the author, a cure was obtained by partial gastric resection. The roentgenographic appearances suggested carcinoma of the distal half of the stomach. In reviewing the literature, it appears that repeated attacks of hematemesis is the most frequent symptom.

BASTECKY, J. AND HOLY, J.: *Contribution to the question of benign gastric tumours.* (Gastro-Enterologia Bohema (Czechoslovak), Vol. I, No. 1, pp. 14-30, 1947).

Most benign gastric tumors do not present clinical symptoms. These appear only when they seat near the cardia or the pylorus or when exulcerations, hemorrhages or additional growth occur. X-ray examination is indispensable for the diagnosis. Six cases are described in detail. One of them was an aberrant adenoma, the other an eosinophilic granuloma, while the rest represented polyps. — O. Felsenfeld.

Bowel

COURTOIS, R., DEWINTER, L., FIRKET, J., GOFFIN, R., GYSELEN, A., MAISIN, J., MICHEZ, J., TILMANT, L., VON DER HOEDEN, R. AND WARMOES, FR.: *Symposium: Jejuno-ileo-cecal tuberculosis.* (Acta G. E. Belgica (continuing Journ. Belge de G. E., Vol. X, No. 4, April 1947, 161-271).

Primary intestinal tuberculosis is rare in this century thanks to hygienic progress and lessening of bovine infection. Primary intestinal tuberculosis may appear in the rare ulcerative form or the well-recognized hypertrophic form, and certain diagnosis rests on finding the Koch bacillus in the stools.

Intestinal T. B., secondary to pulmonary T. B., is common (statistics vary from 15 per cent to 90 per cent of cases of the pulmonary disease) and should be treated as it may undo the good accomplished by collapse therapy and a certain number of cases of the pulmonary disease die of the intestinal complications. It almost always begins in the distal ileum, the ileo-cecal valve or the cecum. Only in a small minority can ulcerations be seen through a rectoscope. The symptoms are variable. Diarrhea occurring in a case of pulmonary T. B. has four chances out of ten of being non-tubercular. The true specific diarrhea is often late in appearing. Secondary intestinal tuberculosis ought to be suspected when the general malaise is out of proportion to the pulmonary involvement. A purely clinical diagnosis is impossible. It gives rise to such general signs as anemia, leukocytosis, decrease of lymphocytes, increased blood sedimentation rate, faulty absorption and hypovitaminosis. The Triboulet reaction (albumin present in stools) has a relative value in diagnosis. X-ray evidence of grave organic entero-colitis in an individual with pulmonary T. B. is equivalent to a positive diagnosis of secondary intestinal tuberculosis. In sanatoria routine repeat G. I. series should be carried out. Complications such as hemorrhages, stenosis and perforations are, relatively speaking, quite rare. Prognosis depends on the pulmonary activity and the extent of the intestinal lesions and the treatment used. In non-treated cases the intestinal lesion may become more serious to life than the lung condition, progressing while the latter improves. In treatment, vitamins (A, B and C) help a great deal. Intestinal resection is advisable where other forms of treatment fail, where the pulmonary disease is stationary and the intestinal lesions are localized and of a serious nature. Operation is imperative in stenosis and perforation. X-ray pictures, physical and hematological check-ups are essential in judging the progress of intestinal T. B.

KUSHNAR, G. R.: *Acute non-specific diarrhea and dysentery.* (Brit. Med. J., May 24, 1947, 717-719).

A great number of detailed observations led the author to believe that chilling of the abdomen or anterior abdominal wall is a common cause of acute non-specific enteritis ashore and afloat in all climates but especially hot climates, and in overcrowded ships. He can see no reason to cling to the widely-held theory of infection, since no specific organisms have been found in these cases. Avoidance of abdominal chilling is the chief point in prophylaxis. Experimental research is needed.

JARVIS, CHARLES: *Pregnancy complicated by acute appendicitis.* (Harper Hospital Bulletin, Vol. 5, No. 3, June 1947, 83-85).

Three cases of acute appendicitis occurring in pregnancy are presented. Operation in these cases is doubly indicated because rupture of the appendix occurs in one of six cases where operation is not performed. Uterine contractions tend to spread any peritonitis that develops and abortion or premature labor almost always results.

POLLARD, H. M., BLOCH, M. AND BACHBACH, W. H.: *Causes and management of anemia associated with ulcerative colitis.* (J.A.M.A., 134, 4, May 24, 1947, 341-346).

109 cases of ulcerative colitis were studied from the standpoint of their anemia. The degree of anemia was related to the iron deficiency present, the nutritional status of the patient, as evidenced by weight loss and the level of serum protein, to the degree of toxemia and infection, the anatomic extent of the disease, the occurrence of exacerbations of the disease, and the sex of the patient, the anemia being more common and more severe in females. Most of the anemias were microcytic and iron provided the best treatment. In normocytic anemias, transfusions and combating the malnutrition were important. No cases of macrocytic anemia were found in this series but they probably would respond to injections of liver extract, as well as folic acid.

COHEN, R. B. AND YAKIS, H.: *Continuous fever of intestinal origin.* (Arch. Int. Med., Vol. 26, No. 6, June 1947, 838-842).

An instance, in which continued fever arises from often unrecognized intestinal diseases, the author cites ulcerative colitis, "right-sided" colitis, cecocolitis, regional ileitis, and diffuse ileocolitis. In the latter, diagnosis rests on finding characteristic x-ray appearances of fecal rigidity and stenosis. Ocular, joint and skin manifestations are common to the group, especially iritis, conjunctivitis, erythema nodosum and thrombosed arteritis. Frequently the abdominal symptoms are overlooked because they are minimal and the patient is regarded as rheumatic.

STARV, RAL: *Hepatodiaphragmatic interposition of the colon with gastric hypertrophy.* (Am. J. Roentgen. & Radium Therapy, 56, 1, 22, July 1946).

Hepatodiaphragmatic interposition of the colon is not a rare entity, and thus it attains sufficient importance so that its symptomatology, course, complications, differential diagnosis and treatment should be gone into with greater thoroughness. Heretofore, investigators have concerned themselves primarily with its etiology and with the reporting of the entity as a rare and incidental finding. The author has included two case reports from the literature to illustrate how real and important the need for thorough familiarity with this entity can be. Next, the gastric symptoms, often found associated with hepatodiaphragmatic interposition, are elaborated upon. A special point is made of stressing the logical association between interposition of the colon and the presence of these gastric findings. The case herein reported is illustrative inasmuch as it demonstrates hepatic pressure upon a hypertrophic stomach. — Franz J. Lust.

REMINGTON, J. H. AND DUCKERTY, M. B.: *Stenosis of the colon secondary to chronic pancreatitis.* (Proc. Staff Meetings, Mayo Clinic, 22, 13, June 25, 1947, 260-264).

Two cases of stenosis of the colon in the region of the splenic flexure by a non-malignant, inflammatory lesion, associated with chronic pancreatitis were successfully relieved by surgery. Only one other case of this kind has been reported in the literature. Clinically and by x-ray the lesion resembled carcinoma of the colon, although in one the roentgenologist recognized its non-malignant characteristics. The lesson to be learned is that colonic stenosis occurring in association with chronic pancreatitis may not be malignant.

FANSLER, W. A.: *Carcinoma of the colon.* (Journal-Lancet, LXVII, 7, July 1947, 263-266).

Bleeding is usually the first symptom and diagnostic rests on x-ray examination. Except in cases of high-grade obstruction, the author prefers single stage operation with open type anastomosis. Sulfas and antibiotics do not prevent peritonitis from late leakage. Early ambulation is advised.

KARSTENS, H. C. AND BAKER, J. A.: *Carcinoma of the colon simulating benign plastic.* (Proc. Staff Meet. Mayo Clinic, Vol. 22, No. 12, June 11, 1947, 234-235).

Two cases are presented in each of which the entire transverse colon was found on x-ray to be involved in a malignant lesion. Operations revealed hepatodiaphragmatic involvement of the transverse colon in both, with extensive involvement of the entire colon in one, and in both stenotic. The question arises, as a result of the finding of these rare lesions, whether a lesion of the benign plastic type can lead its patient on in the large intestine.

CROHN, B. B., GARLOCK, J. H. AND YARNIS, H.: *Right-sided (regional) colitis*. (J.A.M.A., May 24, 1947, 134, 4, 334-338).

In this entity of right sided colitis, the cecum and ascending colon are involved, while the rectum and sigmoid remain free of the disease. It is one cause of unexplained fever and diagnosis is made by x-ray. Complications include ocular manifestations such as iritis, skin complications such as erythema nodosum, inflammation of one or more joints and occasionally endocarditis. Colectomy in suitable cases cures. Medical management, where preferred, involves low roughage diet, vitamins, retention enemas of 1-to-4000 solution of neutral acriflavine, large oral doses of succinyl-sulfathiazole, as well as intramuscular doses of 1 cc. of crude liver extract and vitamin B complex every other day. The disease is characterized by the absence of rectal tenesmus as seen in universal ulcerative colitis or in colitis involving the left side of the colon.

STREICHER, M. H.: *Oral administration of penicillin in chronic ulcerative colitis*. (J.A.M.A., May 24, 1947, 134, 4, 339-341).

Some clinical improvement was noted in 45 patients with chronic ulcerative colitis treated by large daily oral doses of penicillin, although the study concerns itself largely with the effects of penicillin alone or combined with phthalylsulfathiazole on the intestinal flora.

Pancreas

DIVIS, J.: *Pseudocysts of the head of the pancreas with icterus after trauma*. (Gastro-Enterologia Bohemia (Czechoslovak), Vol. 1, No. 1, pp. 8-14, 1947).

A 28-year old woman was shot in the abdomen. The bullet was extracted from the stomach and the opening on the stomach wall sewn up. Four months later the patient developed pain in the right epigastrium and icterus became apparent. A tumor was felt near the pylorus. On operation, a cyst of the head of the pancreas was found. After operation the icterus and the subjective symptoms disappeared.—O. Felsenfeld.

PRESENT, ARTHUR J.: *Aberrant pancreas*. (Am. J. Roentgen. & Radium Therapy, 56, 1, 55, July 1947).

The author tabulates the different abdominal organs in which pancreatic tissue has been found. More than one-fourth of the cases were those with aberrant tissue in the stomach and another fourth with findings in the duodenum.

In the first case reported by Present, the roentgenological examination revealed in the immediate prepyloric region of the stomach a smooth round filling defect on the greater curvature. This defect was movable and seemed small and intramural. Peristalsis did not pass through this area, but the mucosal pattern was seen to change. Gastroscopy did not help in the diagnosis. At operation a firm mass was found on the posterior and interior aspect of the pylorus; ad-

herent to this mass was a cone of tissue which proved to be pancreas. The right half of the pancreatic bed was empty and the left contained what was felt to be pancreatic tissue lying obliquely and pointing up to the stomach.

In the second case the roentgenological examination showed two large areas of diminished density in the barium shadow of the antrum of the stomach. The superior appeared to be a fold of mucosa and could be displaced by palpation. The one on the greater curvature persisted despite manipulation and was well visualized as a polypoid lesion. The entire area was flexible. Gastroscopecally a polyp was seen. At operation a soft, round mass was found proximal to the pylorus.

The true nature of the condition was never recognized preoperatively. — Franz J. Laist

Liver and Gallbladder

STEIN, H. B.: *Laboratory investigations in the differential diagnosis of non-hemolytic jaundice*. (S. Afr. Jour. Med. Sci., Dec. 1946, Vol. 11, No. 4, 139-156).

Since most patients with jaundice are not emergencies in either a medical or surgical sense, a week or ten days may be spent making tests (exceptions are liver abscesses, empyema of the gall bladder, perforation of the gall bladder, hepatic coma due to acute liver atrophy and jaundice due to septicemia). The author employs the van den Bergh reaction; the prothrombin index and its response to synthetic vitamin K, the Takata-Ara reaction, the erythrocyte sedimentation rate, the blood picture and tests relating to urobilin in the urine and feces, and also the hippuric acid test. Rather complete details for carrying out and interpreting these tests are given. A report is made on 192 cases of jaundice in whom the icterus index was above 25, or the serum bilirubin was above 2.0 mg. per cent and these cases were analyzed with reference to the blood count, sedimentation rate, Takata-Ara reaction and prothrombin index. After consideration of the results of these tests in association with clinical findings, it was found possible to make an accurate diagnosis in over 90 per cent of cases, as checked by operation or autopsy. The high value of the paper rests in the author's methods of interpretation of individual tests or combined tests in individual cases.

Therapeutics

PREROVSKY, K.: *Treatment of anal fissures with currents of high frequency*. (Vestnik, Československá Fysiatrické Společnosti (Czech), Vol. 24, No. 6, pp. 124-128, 1947).

The treatment of anal fissures with high-frequency currents becomes easy when glass electrodes with conical endings are used. The current is applied daily, for four to fifteen minutes, increasing the length of the sessions. Good results were observed in 80 per cent of the cases. — O. Felsenfeld.

Increased "Folic Acid" Requirements Resulting from Thyroxin Injection

By
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THE ACTION OF SULFONAMIDES and various other chemicals in producing hypertrophy of the thyroid gland with hypothyroidism has been studied (1, 2, 3, 4, 5, 6). The mechanism of this effect has been attributed to an inhibitory action of sulfanilamide on the conversion of inorganic iodine to diiodotyrosine and to thyroxin (7). Williams and Bissell (8) independently demonstrated reduced protein bound iodine following treatment of cases of thyrotoxicosis with thiouracil, which indicated inhibition of the introduction of iodine into the organic molecule.

Granulocytopenia and anemia in rats fed sulfonamides in purified diets (9, 10, 11) has been regarded as independent of the anti-thyroid activity of these compounds. The existence of a "folic acid" deficiency in rats fed sulfonamide containing diets has been demonstrated (12, 13) and the cure of the granulocytopenia with "folic acid" has been reported (14).

METHODS AND RESULTS

In the course of a series of investigations on this subject, two sulfonamides were used: succinylsulfathiazole and sulfaguanidine. These compounds were used at levels of 1 and 2% in stock diets and in a highly purified synthetic diet (13). Table I presents the results obtained with various diets and various supplements.

From these values, it can be seen that the subcutaneous injection of 10 gamma of thyroxine daily to rats on "folic acid" free diets did not alter the degree of leucopenia. On the other hand, thyroxin given rats on sulfaguanidine-containing stock diets precipitated an acute leucopenia which seemed to be prevented by diiodotyrosine. Further, the simultaneous oral treatment of the rats on the synthetic sulfonamide diet with "folic acid" concentrate and the subcutaneous treatment with thyroxin resulted in nullification of the tendency toward the development of leucopenia. The "folic acid" concentrate was prepared according to the method of Hutchings, Bohonos and Peterson (23). It was fed at levels of 2 mg. daily for two weeks. This combination of facts leads to the conclusion that thyroxin and the concomitant high metabolic rate increase the demand for "folic acid." On the stock sulfonamide diet, there is a marginal intake of "folic acid" from the diet. It is made marginal because the intestinal synthesis of this factor is reduced.

Peters and Rossiter (15) found that hyperthyroidism causes a fall in tissue cocarboxylase and free thiamine. It was certain that excess thyroxin increased the need for thiamine. Drill and Overman (16) found

that rats lost weight when fed thyroid and that this loss could be stopped by thiamine administration. In order to gain weight, pyridoxin and pantothenic acid were needed. Drill (17) had first disclosed the existence of an antagonism between thyroxin and thiamin. Involvement of riboflavin in this thyroxin interrelationship with B complex factors was demonstrated

TABLE I
Leucopenia in Rats on Sulfonamide Containing Diets —
Treated and Untreated

DIET	Time on Diet	Subcut. Thyroxin 10 ug. daily	Oral Diiodotyrosine 100 ug. daily	Thyroid mg/100 g.	White Count	Value average for rats
Stock Diet + 2% Sulfaguanidine	10 weeks	—	—	32	8500	4
Stock Diet + 2% Sulfaguanidine	10 weeks	+	—	12	5500	9
Stock Diet + 2% Sulfaguanidine	10 weeks	—	+	35	10000	6
Stock Diet + 2% Succinylsulfathiazole	10 weeks	—	—	10	9000	4
Stock Diet + 2% Succinylsulfathiazole	10 weeks	+	—	10	4700	4
Stock Diet + 2% Succinylsulfathiazole	10 weeks	—	+	12	10200	4
Synthetic Diet + 0.5% Sulfaguanidine	6 Months	—	—	14	5900	5
Synthetic Diet + 0.5% Sulfaguanidine	6 Months	+	—	15	6400	4
Synthetic Diet + "Folic Acid"	6 Months	—	—	12	10200	5
Synthetic Diet + "Folic Acid"	6 Months	+	—	11	11000	6
Stock Diet + 1% PABA	10 weeks	—	—	15	6900	6
Stock Diet + 2% PABA	10 weeks	—	—	23	5100	6

* Treatment with "Folic Acid" for a two week period before examination.

(18). Thyroxin secretion with increased intensity of general metabolism (19, 20, 21) necessitated increased thiamine intake. Now, the increased demand for B complex factors caused by thyroxin can be extended to "folic acid."

There is no direct relation between the production of hypertrophied thyroids with hypothyroidism (produced by sulfaguanidine in the diet) and the leucopenia produced. Succinylsulfathiazole produces a marked "folic acid" deficiency with consequent leucopenia but no thyroid changes are seen. With sulfaguanidine, there is produced a less marked "folic acid"

deficiency and the thyroids are greatly enlarged. p-Aminobenzoic acid as shown in Table I produced both thyroid hypertrophy and leucopenia. Similarity of action of p-aminobenzoic acid and sulfonamides was pointed out previously (22).

SUMMARY

Thyroxin increased the requirements of "folic acid" in the rat. This is reflected in the leucopenia seen in rats on diet low in "folic acid," injected subcutaneously with thyroxin.

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The Effect of Short-Wave Diathermy on the Secretory Activity of the Fasting Normal Human Stomach

By

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AN UNDERSTANDING of the influence of short-wave irradiation on the secretory physiology of the normal human stomach is a prerequisite to the clinical use of diathermy on the upper gastrointestinal tract. If the quantity or quality of gastric secretion is, in truth, important in the genesis or aggravation of peptic ulceration, or if the hypacidity or achlorhydria observed in certain of the gastritides is of clinical significance, it behooves the clinician to look into this matter before he prescribes short-wave treatment to the upper abdomen.

Clinical experience with diathermy in the treatment of peptic ulcer has been accumulated in an unconvincing manner by certain German investigators (7, 10, 11, 12). These reports are replete with opinions; data are sparse. They include little information regarding secretory effects.

The present study was initiated prior to an investigation of the clinical application of diathermy in certain of the gastritides. An effort was made to determine the effect of diathermy, as it would be applied in clinical use, on the rapidity of total gastric secretion in the normal stomach, and on the free and total acid contents of this secretion. It was felt that observations on the activity of the gastric chief cells would give information of little practical or theoretical value.

HISTORICAL

The earliest observations on the effect of temperature on the secretory work of the stomach were those

of the Army physician, William Beaumont (2). He noted that febrile states in his subject with a gastric fistula caused drying of the exposed gastric mucosa and suppression of secretions, including that of mucus, even after application of secretory stimulants.

Meyer, Cohen and Carlson (13) in 1918 studied gastric secretion in dogs during artificially induced fever. Although Gluzinski (8) had concluded in 1888 that during chronic fevers the toxicity of infection is more potent in suppressing secretion than elevation of temperature, these investigators found that hot-box induced fever in itself diminished secretory rate and concentrations of total and free acid. Gastrin did not induce secretion while the temperature was elevated. Most important for the present study, they concluded that it is the elevation of body temperature alone which controls secretion because externally applied heat produces the same effects as fever following injection of foreign protein. They suggest that, "... during fever, toxins are elaborated having a direct depressor action on the cells of the stomach so that they fail to react to the secretory nerve impulses and to the secretagogues."

Two important investigations have been published on certain experimental aspects of the problem. Brody (5) in 1927 studied the effects of diathermy upon canine gastric acidity, using various milliamperages and voltages. Fasting dogs under atropine sulfate, morphine and ether anesthesia were treated by contact epigastric and intragastric active electrodes. No medication was used while the gastric specimens were being withdrawn. Increased appetite was noticed on

about the fifth or sixth day after diathermy treatment. Following diathermy, many of the animals were autopsied; except for "slight enlargement of the liver," no gross or microscopic pathology was found in any organ. As a result of this work, Brody concluded that subsection of the stomach at frequent intervals to diathermy of low milliamperage and medium voltage over long periods results in increased gastric acidity. High milliamperage and medium voltage treatment, although immediately producing high acid levels, eventuates in a period of secretory depression.

Stewart and Boldyreff (16) in 1929 made an experimental study of the effects of diathermy on canine gastric secretion, using 16 dogs with various types of gastric fistulas and pouches. In most of the dogs observations were made on empty stomachs. Skin contact electrodes, 4 by 6 inches, with 400 to 1400 milliamperes and duration of application up to one hour, were used. The greatest temperature change observed in the stomach during application of the current was 1.4° C, with average temperature rises from 0.5° to 1.0° C. In from five to ten minutes after the heat was discontinued, the gastric temperature had returned to normal. They found that diathermy stimulates canine gastric secretion when the stomach is in a state of rest or during psychic or chemical phases of secretion; however, when "chronic gastric catarrh" was present no such stimulation was obtained. The stimulated juice was higher in acid and lower in pepsin than that of the resting stomach. During the psychic and chemical phases of secretion, diathermy notably increased the rate of secretion.

Important observations on the human stomach began when Bauer (1) in 1935 conducted experiments on the effects of short-wave diathermy on human gastric acidity. In 16 of 20 patients acidity was diminished, while in the other four it was increased. The volume of secretion was decreased in seven of 16 subjects, increased in four, and not appreciably affected quantitatively in five. The author concluded that secretory changes could best be explained merely by the local heating effects.

Brunner-Ornstein (6) in 1936 made the statement that diathermy results in an increase of 30 to 40 per cent in the acid production of normal human stomachs after alcohol test meals. She presented no data.

In 1937 Neidhardt and Schlinke (14) observed increased secretion by the human stomach following five minutes of six meter diathermy treatment. Ten of their patients had normal stomachs, two chronic duodenal ulcer, and two hypochlorhydria.

Benassi and Montagnini (3) in 1937 observed the effects of diathermy on 19 patients with abnormal secretion. In almost all cases the treatment resulted in good analgesic effects, with improvement of gastric symptoms. In six of eight patients with hyperchlorhydria, diathermy resulted in improved or normal acidities. In four cases of histamine-resistant achylia there was no improvement. On the other hand, in five of seven patients with hypochlorhydria, gastric secretion was brought from low values to normal.

A warning is voiced in the findings of Skorpil and Uldrich (15) concerning the possibility of granuloma

production as a result of diathermy treatment. These authors described four cases of lipophagic granulomata of the epigastric region which followed short-wave application and which were ascribed to this treatment.

MATERIAL

Ten healthy adult human volunteers were used. None had gastrointestinal symptoms or history of gastrointestinal complaints. There were no evidences of nutritional deficiencies. Prior to the study four of the volunteers had gastrointestinal X-ray series and gastroscopic examinations; these studies were normal except for a duodenal diverticulum in volunteer No. 1. The ages varied from 19 to 42 years. There were four females. All were of the white race. Six used alcohol and seven tobacco.

METHODS

Each of the ten volunteers was studied on six days, not necessarily consecutive. Nothing was taken by mouth after midnight before the day of each test, and food, drink and tobacco were interdicted until the completion of each day's test. Thus the stomach was studied in the fasting state.

On each of the six days the stomach was emptied as completely as possible by aspiration four times, at 8, 9, 10, and 11 AM. The Levine tube was withdrawn after each aspiration.

For the first three days the aspirations were taken from each volunteer without interruption, in order to obtain a normal fasting curve in each case. For the last three days the aspirations were taken and tested as usual, but immediately after the 9 o'clock specimen was removed, the volunteer was given 30 minutes of diathermy over the gastric region. Crystal-controlled machines, producing 22 meter waves at 13.66 megacycles, were used; the milliamperage was set at 175. The drum was centered over the subcostal margin two inches to the left of the midline, with the volunteer in the supine position.

The volume of each of the four daily specimens was measured. Each specimen was strained through gauze, and 10 ml. was then titrated with N/100 sodium hydroxide for free and total acid content. Topfer's solution and phenolphthalein were used as indicators. Acidities were expressed in terms of Clinical Units.

RESULTS

The findings expressed as averages of the three day determinations — three days without diathermy and three with, in the case of each volunteer — are given in Tables I, II, and III. Consideration of the figures reveals that diathermy did not significantly affect the gastric volume or free or total acid content. Statistical evaluation is not necessary.

DISCUSSION

In spite of published recommendations for expression of gastric acidities in terms of pH (9), it was felt that for present purposes the cruder but nevertheless accurately determined Clinical Units would be most useful because they best parallel the crude fac-

TABLE I

Three-day averages of gastric volumes (in ml), without and with the influence of diathermy in each of 10 volunteers

Volunteer	8 AM	9 AM	10 AM	11 AM
1	44.3 46.0	44.0 37.7	31.0 31.3	42.3 52.7
2	40.0 33.0	27.0 27.0	23.0 22.7	23.3 24.3
3	32.7 34.7	22.3 34.3	25.0 24.0	16.0 26.3
4	12.3 12.0	17.0 10.0	16.3 11.7	20.0 12.3
5	29.0 26.3	32.0 29.0	22.3 17.3	32.7 47.0
6	45.3 32.0	28.3 25.7	37.0 41.3	24.0 17.7
7	26.3 26.0	10.0 12.7	5.7 7.3	7.0 7.0
8	17.7 16.3	5.3 8.7	5.0 8.3	5.0 4.3
9	33.3 33.7	25.7 26.3	32.0 26.7	31.0 23.3
10	30.3 36.7	35.0 35.7	35.3 29.7	28.7 36.3

TABLE II

Three-day averages of free acids (in CU), without and with the influence of diathermy in each of 10 volunteers

Volunteer	8 AM	9 AM	10 AM	11 AM
1	59.0 50.7	57.0 50.3	64.3 48.0	69.0 45.7
2	47.7 38.7	59.0 36.3	66.7 39.3	60.7 39.0
3	2.0 0	0 0	0 0	0 0
4	0 0	0 0	0 0.7	0 1.7
5	19.3 22.3	27.0 26.0	13.7 12.0	20.0 13.0
6	20.7 23.3	18.0 10.3	15.7 16.7	12.0 6.0
7	5.0 0	0 3.0	2.3 3.7	3.3 0
8	6.7 0	0 8.0	5.0 0	0 0
9	29.7 27.7	25.7 28.0	28.7 ⁽¹⁾ 23.0	25.3 25.0
10	15.3 18.7	18.0 15.0	13.4 19.0	18.0 17.3

tors involved in gastric analysis, namely, the unmeasurable biliary reflux, gastric mucus secretion, periodic gastric emptying, and swallowed saliva. Thus false security is avoided. It is gratifying in this connection to note Bockus' statement (4), "To date, no clinical significance can be attached to an accurate measure of the relative amounts of acid and nonacid juices entering the stomach." It was felt that the determinations in the present study were accurately arrived at, but

TABLE III

Three-day averages of total acids (in CU), without and with the influence of diathermy in each of 10 volunteers

Volunteer	8 AM	9 AM	10 AM	11 AM
1	74.7 71.2	72.7 62.7	51.0 64.3	75.7 61.7
2	71.0 59.0	74.0 56.7	56.7 57.7	73.7 58.1
3	9.3 8.0	5.3 8.0	4.7 5.7	4.7 5.0
4	7.7 12.0	8.0 9.0	10.3 9.3	7.7 12.3
5	33.7 34.0	42.3 39.3	24.7 24.3	27.0 25.3
6	66.0 49.0	46.0 50.3	37.7 44.0	27.7 26.3
7	37.3 22.3	13.0 23.3	27.7 31.0	34.3 23.7
8	21.3 18.7	8.0 11.7	14.0 11.3	7.3 7.7
9	41.0 40.3	36.7 37.7	28.0 32.7	29.0 40.3
10	28.7 44.0	50.3 44.7	39.3 46.7	44.7 44.3

that the results must be interpreted with the interfering external factors in mind.

There was considerable variation in the serial determinations in most of the cases, variation which is still evident after they are smoothed out by conversion to three-day averages. Tendencies can be found one way or the other when the figures from a single volunteer are considered. Because such tendencies occur in the figures of the 8 and 9 AM aspirations as well as in those of 10 and 11 AM, they must be due to the inherent vicissitudes of gastric secretion, and not to the external influence of diathermy. It is felt that any conclusion that diathermy influences gastric secretion must be based on a tendency which is not only marked but constant in the majority of cases tested. It may be that previous investigators (1, 3, 6, 14) have preferred to interpret such minor variations as due to diathermy effect, but such a conclusion cannot necessarily be accepted in the absence of published data.

In the present study it so happened that there were two volunteers who met the criteria of hyper-secretors and two who were relative hyposecretors — variations of normal. The determinations in these cases did not behave differently than those in the other six.

Although it is recognized that the findings in these normal persons are not necessarily applicable to patients with peptic ulcer or gastritis, it may be that diathermy need not be withheld in the treatment of such patients because of the fear of increasing acid production. Similarly, however, treatment of such cases in the hope of decreasing secretion may not necessarily help the situation.

CONCLUSIONS

As a result of studies on ten healthy volunteers, it is concluded that short-wave treatment, as applied here, has no demonstrable effect on the total secretion.

or free or total acid production of the normal fasting stomach.

ACKNOWLEDGMENT

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Submucous Lipoma of Transverse Colon with Intussusception

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SUBMUCOUS LIPOMATA of the intestinal tract are rare. Many general practitioners and medical doctors do not know that such benign tumors in the intestinal tract occur. Most surgeons have not operated upon more than one or two cases during their lifetime. This rarity is best confirmed by the fact that in the Mayo Clinic, among 3,924 consecutive autopsies, only 25 intestinal lipomata were found, i.e., 0.6 per cent. Kirschbaum reviewed 5,724 autopsies and found only 0.2 per cent submucous lipomata while Staemmler, among 17,000 necropsies, found 0.05 per cent.

The first complete analysis of the literature on submucous lipomata from all portions of the gastrointestinal tract was published by De Witt Stetten in 1909. He reported 77 cases, among them two of his own. The next comprehensive review, by Comfort in 1931, collected from all sources, reported about 181 cases, including Stetten's cases. In 1937, Pemberton and McCormack collected 97 cases with symptoms plus 19 cases found at autopsy, making a total figure of 116. There were a number of other reports in the literature collecting submucous lipomata at or below the ileocecal valve, including Poston's report of 121 cases in 1934, and Gault and Kaplan's report of 130 cases in 1941. The most recent report of George T. Pack and Robert T. Booher on "Intussuscepting Submucous Lipoma of Right Colon" collected 153 cases from the ileocecal valve to the rectum.

From this short summary of the more comprehensive reviews of the literature, it is evident that these cases are not too frequent, and therefore, I would

like to report my own case, which was presented at the meeting on May 5, 1947 of the Rudolf Virchow Medical Society in New York. This case was presented just a few days before the publication of the interesting paper by Pack and Booher.

CASE REPORT

The patient was a 52 year old white housewife. Her previous history revealed only the usual childhood diseases; otherwise she had always been healthy. She had three healthy children and had been in menopause for the past few years. When I first saw her in November, 1946, she complained of severe pains in the middle of the abdomen. At the first consultation I found, on pelvic examination, a large fibroid of the uterus going up almost to the umbilicus. I recommended hysterectomy. In view of the fact that the character of the pain could not be explained totally by the fibroid, a G. I. x-ray series was done after her admission to the hospital. The impression of the X-Ray Department was, "Large pelvic mass which is either uterine or ovarian in origin. Area of calcification within the mass along its left border, hiatus hernia, no evidence of organic lesion in the gastrointestinal tract." I must admit that the G. I. series was followed up for only 24 hours, when the barium had reached the cecum.

Physical findings at admission: The lungs, heart and urine were negative. Her blood pressure was 140/90. Laboratory tests: Urine had a specific gravity of 1.024; albumin, sugar and acetone negative. The erythrocyte count was 5,200,000, hemoglobin 94 per cent, leucocytes 13,900 with 5 eosinophiles, 3 myelocytes, 2 stab polymorphonuclears, 76 segmented polymorphonuclears, and 14 lymphocytes. The sedimentation rate was 17 M. M. in 60 minutes. On the fourteenth of December, a supra-vaginal hysterectomy with removal of both adnexae was done. The pathologist reported fibromyoma of the uterus.

The post-operative course was uneventful but shortly after her discharge from the hospital on December 26th,

cramp-like pain in the abdomen started with irregular intermittency, at times the intervals between attacks being long and at other times short. On January 18, 1947, the patient was examined in my office again. Her complaints at this visit were that the cramp-like pains had increased considerably and had become much more frequent.

On examination, a slight distention of the abdomen was obvious and a mobile tumor was palpable just above the navel. X-ray studies after barium enema two days later revealed that "The enema flowed rapidly to a level slightly beyond the splenic flexure, where complete obstruction was encountered resulting in some dilatation of the bowel distally (Figure 1). The post-evacuation

palpated in the transverse colon itself. The tumor was about the size of a hen's egg. The transverse colon was opened with a longitudinal incision. The large, partially



Figure 1 — Barium enema of reported case, full filling.

film clearly demonstrated the presence of a large polypoid tumor mass in the distal transverse colon resulting in fusiform dilatation of this section of the bowel and clearly demonstrated the etiology of the obstruction to the flow of fluid. Impression: Large polypoid tumor of distal transverse colon, probably adenocarcinoma" (Figure 2).

My own impression after seeing the x-ray studies was polypoid tumor with intussusception and chronic obstruction. Therefore, the patient was admitted to the hospital again on January 21, 1947.

Physical findings: The lungs, heart and urine were the same as at the previous admission. Her blood pressure was 190/100. Laboratory work: The erythrocyte count was 3,960,000, hemoglobin 81 per cent, leucocytes 17,250 with 3 eosinophiles, 83 segmented polymorphonuclears, 6 lymphocytes and 8 monocytes. On January 23, 1947, the patient was operated upon. Under spinal anesthesia the abdomen was opened with a left-sided inter-rectal incision mostly above the navel and extending about one inch below the navel. A rather large amount of clear exudate was present in the abdominal cavity. A mobile tumor of the transverse colon was identified as an intussusception of about two and a half inches. After reduction of the invagination a large polypous tumor could be



Figure 2—Barium enema of reported case after evacuation.



Figure 3 — Gross specimen of reported case.



Figure 4—Gross specimen of reported case cut in half.



Figure 5—Microscopic slide of reported case (low power).

gangrenous polypous tumor was removed at its infiltrated pedicle. After the removal of the tumor the wall of the colon where the pedicle had been attached was very thin. This spot was therefore covered from outside by a two layer sero-serosa suture followed by careful reconstruction of the mucous membrane from the inside with fine catgut sutures. The infiltration of the pedicle was considered as only inflammatory and non-malignant, while the character of the cauliflower-like polyp could not be recognized. At any rate, it was felt that we were confronted either with a benign tumor or with a localized malignancy and that removal at the pedicle was sufficiently radical to take care of every eventuality. Therefore, after the tumor was removed, the longitudinal incision of the colon was closed transversely by a three layer suture, mucosa and musculature with continued fine catgut and the serosa with interrupted fine black silk. The abdomen was then closed in layers. As a safety measure a cecostomy was performed from a McBurney incision.

The post-operative course was uneventful with the exception of a slight infection of the left inter-rectal incisional wound. On February 11th the cecostomy was closed. On February 22nd the patient was discharged in good condition.

The pathological report was as follows: "Specimen consists of a rather large ovoid tumor mass partially covered by colon mucosa. Most of the surface presents a dirty degenerated grayish-green material with several ulcerations. The base of the tumor is somewhat excavated and appears to be the pedicle to which it was attached to the colon. The entire mass measures 8 cm. in length, 6 cm. in width and 4 cm. in depth. Cut section reveals the typical fatty lobules of benign lipoma. It appears to originate from the submucosal area" (Figures 3 and 4).

"Microscopic: Histological section at the junction of the tumor and the mucosa reveals a typical lipoma

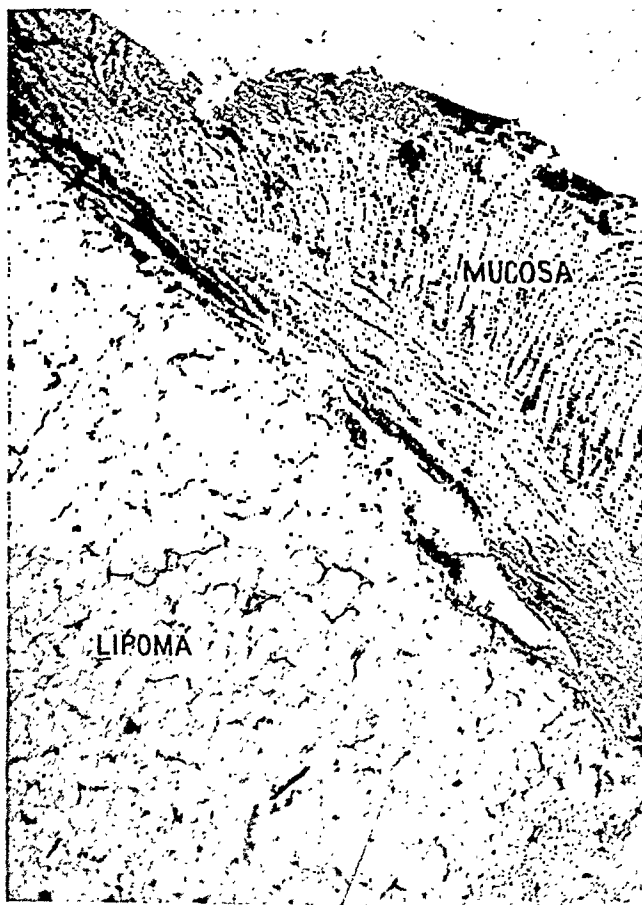


Figure 6—Microscopic slide of reported case (high power).

breaking through the normal colon mucosa to cause an ulceration. At the surface there is an inflammatory cell reaction but there is no evidence of any malignant degeneration. The lipoma itself consists of the typical fat cells in a lobulated pattern" (Figures 5 and 6).

COMMENT

Lipomata in the gastro-intestinal tract occur most frequently between the ages of 40 and 60, in other words, at the cancer age. In the colon, cancer is the most frequent malignant tumor while adenomatous polyps are the most common benign tumors. Lipomata are next in frequency to polyps. They occur more in women than in men. They are usually single, but may be multiple. They can be sessile or pedunculated. They are rounded or ovoid. They arise from the fat in the submucous layer of the intestine and grow inward into the lumen. They may never produce symptoms. They may occur anywhere in the alimentary tract. Comfort reported 92 in the large bowel, 65 in the small bowel and 22 in the stomach. The locations in the large bowel are the cecum, ascending colon, sigmoid flexure, transverse colon, rectum and descending colon and the frequency is in the order in which they are enumerated. Those which produce symptoms show mostly the clinical picture of a chronic intestinal obstruction without particular time intervals, characterized by distress, distention and paroxysmal pains associated very often with nausea or vomiting. Frequently, blood is present in the stool. The other clinical picture may be that of an acute intestinal obstruction, mostly caused by an intussusception, although intussusception can produce, as in my own case, the symptoms of only a chronic obstruction.

In cases where the surface of the tumor is eroded, a slow hemorrhage with blood in the stools will be present, causing various degrees of anaemia.

At times the pedicle can become twisted with a strangulation of the tumor. This is very rare because the pedicle is usually very thick and cannot be easily twisted. As far as I could discover in the literature, there was not one case in which a submucous lipoma had become malignantly degenerated. Most of the cases reported in the literature have been considered as malignant tumors until the specimen was actually sectioned and its true nature seen. Therefore, in the majority of cases, resections in one or two stage procedures were done although a simple excision could have been performed.

Relatively few cases of a simple excision with primary repair of the bowel, such as I have done in my case, are reported. In certain cases of intussusception a severe involvement of the bowel wall can demand resection procedures even if the tumor itself could be recognized as benign.

With the advancement of x-ray studies, especially with the evaluation of the film after evacuation with or without air inflation, showing the mucosal pattern, it should be possible to make the diagnosis preoperatively more frequently.

SUMMARY

A case of a submucous simple lipoma of the transverse colon with obstruction and intussusception is reported.

A short review of the clinical picture and the pathology is given.

The purpose of the demonstration is to remind the diagnostician, as well as the surgeon, that among the tumors of the intestinal tract are benign simple lipomata, which can be treated with simple excision and primary repair of the bowel.

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The Importance of the Vi Antigen

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SALMONELLAE are gram negative microbes causing Salmonella fever (typhoid-like disease), septicemia, gastroenteritis or symptomless carrier state in man. These organisms are characterized by certain antigenic structures which fit into a pattern known as the Kauffmann-White-Edwards scheme. This scheme is based upon body antigens, which are resistant to heat and alcohol but not to formol, and are called group, or "O" antigens. The other type of antigens, associated with the flagella, are resistant to formol but not to heat or alcohol and are designated as "H" antigens. The types of Salmonella are differentiated with the aid of antigenic analysis, currently called "Salmonella typing." While approximately 150 Salmonella types are known to date, about 95% of Salmonella infections are caused by not more than 15 strains, among which Salmonella typhimurium, S. paratyphi B., S. derby, S. cholera-suis, S. montevideo, S. oranienburg, S. newport, S. typhosa, S. panama and S. anatum are most important in the United States.

Salmonella infections with grave clinical syndromes are frequently due to S. typhosa, S. cholera-suis and the paratyphoid bacilli. S. cholera-suis is always propagated from animal to man, often causing deadly septicemia. Its spread may be checked by sanitary measures preventing food contamination. S. typhosa and the paratyphoid organisms most frequently produce Salmonella fever. While the paratyphoid organisms occur in geographically more or less circumscribed areas, typhoid fever is found everywhere where sanitary conditions are favorable for its propagation. Typhoid fever is a serious menace in cities having a bad water system and to rural areas where its spread is due to the contamination of wells and food. Typhoid fever is originated only by humans and their excreta. It is one of the earliest known human salmonellosis and attracted attention because of the high mortality rate (about 10%) and uniform clinical picture. The advent of World War I gave considerable stimulus to research in typhoid fever as the movement of large numbers of military personnel and civilians, together with inadequate sanitary conditions, began to point out specific difficulties. It was discovered that freshly isolated strains of S. typhosa failed to agglutinate with specific "O" sera. It was also found that the reaction to vaccination was, in some instances, severe, but the immunity afforded, while satisfactory to a certain extent, still left room for improvement. Many studies were carried out employing various modes of vaccine preparation to find a reliable method, none of which gave more protection

than the original means involving the use of heat killed and phenol preserved organisms. This method of vaccine preparation destroyed the "H" antigen and utilized the "O" antigen alone.

It was not until the discovery by Felix and Pitt (1) of a new antigenic component that a road was opened whereby steps could be taken toward the goal of better diagnosis and prophylaxis of typhoid fever. The new antigen was called the Vi antigen (for "virulence"). This antigen was present particularly in freshly isolated strains. Felix and Pitt (1) stated that S. typhosa containing the Vi antigen is of greater pathogenicity to mice than strains without this factor. Later experiments by Almon and Stovall (2) and Kauffmann (3) confirmed this report. Though the "O" antigen of S. typhosa co-exists with the Vi antigen in newly isolated strains, the presence of the latter prevents "O" agglutination from taking place. This inhibiting action is probably due to the location of the Vi antigen on the surface of the organisms as found by Bhatnagar et al. (4) which "covers" the deeper situated "O" antigen. This explains the difficulties encountered in agglutination experiments involving anti-O sera and organisms with Vi antigens.

The Vi factor is unstable. Simple sub-cultures on routine media result in the progressive loss of the Vi antigen. Storage at room temperature, heat and many chemicals cause its complete destruction. Absolute alcohol, acetone, and glycerin (Peluffo) (5) preserve the Vi factor. The instability rendered experimentation difficult. Culturing without antigenic loss is possible only on egg slants followed by storage at ice-box temperature. Another means consists of culturing Vi strains in broth to which anti-O sera has been added.

Terminology was initiated by Kauffmann (6) to cover the loss of various characteristics of the Vi antigen. If the culture contained Vi antigen and could not be agglutinated by anti-O sera, he termed it "V" for "viel" (much). After ability to agglutinate in the anti-O serum was gained while still retaining certain Vi properties, the culture was said to be undergoing "V-W" variation. When all the Vi characteristics were lost, the culture was termed "W" for "wenig" (little). As this variation takes place, the loss of immunologic properties occurs in a successive manner. Almon (7) listed the changes as taking place in the following way:

1. Acquisition of O agglutinability.
2. Decreased ability to stimulate the production of Vi agglutinins in measurable amounts in rabbits.
3. Decreased ability to agglutinate in anti-Vi serum.
4. Decreased ability to absorb Vi antibodies from anti-Vi serum.

It may be pointed out that according to Bhatnagar

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(8) there is an increased susceptibility of the "W" cultures to phagocytosis and that in the variation from "V" to "W," bacteriophage sensitivity is usually lost. The phenomena observed during "V-W" variation is not due to the development of roughness, as both "V" and "W" cultures are smooth. Colonies of the "V" form differ from pure "O" forms morphologically also, the first being the more opaque of the two.

The presence of the Vi antigen has been reported from other *Salmonellae* than *S. typhosa*. Many strains of *S. paratyphi* C contain the Vi antigen (Kauffmann, (9), Ogonuki (10)). Hayes and Freeman (11) found that all *S. paratyphi* C strains isolated in India during the last years contained this antigen. A rare *Salmonella*, known as *S. ballerup*, and the recently described *S. hormaechei* and *S. exeter* also contain Vi antigen. The Vi antigen present in certain *E. coli* strains is, according to Bekker and Vink (12), identical to the Vi antigen in *S. typhosa*. Luippold (14) published findings confirming this report. Longfellow and Luippold (13) proved that the Vi antigen of *S. ballerup* is also identical to that of *S. typhosa*. Checacci (15) stated that the Vi antigen of *S. ballerup* is the same as that of *S. paratyphi* C. Ogonuki (10) found that the Vi antigens of *S. typhosa* and *S. paratyphi* C do not differ from each other. These findings prove that there is no detectable difference in the Vi factors contained by different *Enterobacteriaceae*. There is, however, a difference in the sensitivity of different strains to various specific bacteriophages.

Practical application of this abundance of theoretical information concerning the Vi antigen was not long in developing.

Methods for employing Vi cultures in the diagnosis of typhoid fever were devised. Brower (16), and Gunther (17) published surveys evaluating the present state of such methods. Gunther (17) and others use the so-called Bhatnagar strain of typhoid bacillus in preparing stable Vi antigens. Much hope was attached to the Vi agglutination, chiefly in the detection of typhoid carriers. Several authors, among them Soman (18), found, however, that at least 5% of the population who are not carriers of typhoid bacilli show a positive Vi agglutination test, while the sera of as many as 10% of typhoid carriers do not give a positive test. In our own experiments with Vi agglutination tests, the sera of seven cases of typhoid fever, 131 chronic typhoid carriers, 107 persons immunized with typhoid vaccine and 112 other individuals were tested for the presence of the Vi antigen, using the Bhatnagar (19) technic, were examined during the last five years. Of the cases and carriers, 101 harbored organisms belonging to the types A, C, E and F of *S. typhosa*; 27 were untypable and no typing was attempted in three instances. Agglutination with the Vi antigen to the critical titer 1:20 or in higher dilutions was observed in none of the cases; 113 of the carriers (86.2%); nine of the immunized persons (8.4%), and 12 of the controls (10.7%). Thus we were not able to demonstrate the superiority of the Vi agglutination test over bacteriologic methods. These findings are in accordance with the opinion of Soman (18) and others, who consider "O" and "H"

agglutination, together with bacteriologic culture, of greater value for the diagnosis of salmonellosis.

The use of the Vi antigen in the prevention and treatment of typhoid fever gave more uniform results.

Felix (20, 21) and the group of Luippold and Longfellow (13, 14), worked out methods for the utilization of the Vi antigen in the prophylaxis and therapy of typhoid fever. The Felix vaccine contains 22.5% alcohol as a preservative. Luippold (14) injects the Vi antigen separately, while Felix recommends immunization with a T.A.B. (typhoid, paratyphoid A and B) vaccine in which the Vi antigen is preserved. Animal experiments proved the value of these vaccines. Serial inoculation of human volunteers testify that the Vi vaccine does not cause untoward reactions in man. In our own experience, 50 volunteers were immunized according to the schedule of Luippold, 50 with the Felix vaccine and 60 with the routine T.A.B. vaccine. While all of the persons immunized with the Vi vaccines developed mouse protecting antibodies to a titer higher than 1:10, seven out of the 60 individuals inoculated with T.A.B. alone failed to produce such antibodies.

The anti-Vi serum is widely used, mainly in the Mediterranean area and in South America. The results are encouraging.

While engaged in studies of the Vi factor in *Salmonellae*, the question arose as to why typhoid bacilli containing these factors are more important than pure "O" strains in the pathogenesis of typhoid fever. As stated above, *S. typhosa* possessing Vi antigen is of greater pathogenicity for mice than organisms devoid of this factor. The immunobiologic responses in typhoid fever and the behavior of the causative organism *in vitro* suggest that the presence of Vi antigen is of great importance in the beginning of the infection and during the first stages of its propagation. Experiments were, therefore, set up with typhoid and paratyphoid C organisms, with and without the Vi antigen, both *in vitro* and in experimental animals, to discover the role of this antigen in human salmonellosis.

Five strains of *S. typhosa* and two strains of *S. paratyphi* C were employed in these experiments.*

The strains were maintained on egg-slants at ice-box temperature. They were seeded to tryptose agar before use. "V" colonies were selected and inoculated into broth containing 1:10,000 anti-O serum. Simultaneously "W" colonies were picked and inoculated into tryptose broth with 1:10,000 anti-Vi serum. After repeating the plating and broth cultures three times, growth consisting of pure "V" and "W" types, respectively, was obtained. These pure cultures were used for further studies.

IN VITRO EXPERIMENTS

The growth curves of pure "V" and "W" types derived from the same strains were determined. Inocula containing $1,000 \pm 38$ micro-organisms were added to 25 cc. of sterile tryptose broth, pH 7.2. Samples were taken after 4, 8, 24 and 48 hours and

* The authors are much indebted to Drs. P. R. Edwards, F. L. Mickle, K. M. Wheeler and A. Juenker for most of these strains.

the number of the micro-organisms determined by the plate count method. Four such experiments were carried out with both the "V" and "W" types of each strain. Table No. I shows the results of the experiments. The values found after 8 and 24 hour cultures are given in this table. The results are evaluated with the aid of the "t" test. For brevity's sake only the average bacterial counts, the "t" values and the corresponding probabilities of the goodness of fit are given. This statistical evaluation indicates that organisms with the "V" factor multiply faster during the first part of the growth curve than organisms without the Vi antigen.

TABLE I
MULTIPLICATION OF SALMONELLAE WITH VI ANTIGEN IN VITRO

Salmonella	Time	No. of organisms from culture of Vi form	O form	t	P approx.
<i>S. typhosa</i>					
Watson	8 hours	748x10 ³	613x10 ³	1.717	.15
	24 hours	427x10 ³	403x10 ³	<1	>.3
Bhatnagar	8 hours	938x10 ³	547x10 ³	4.478	.005
	24 hours	501x10 ³	483x10 ³	<1	>.3
strain 3	8 hours	423x10 ³	319x10 ³	2.513	.05
	24 hours	356x10 ³	370x10 ³	<1	>.3
strain 4	8 hours	514x10 ³	329x10 ³	3.127	.02
	24 hours	347x10 ³	318x10 ³	1.146	.3
strain 5	8 hours	339x10 ³	308x10 ³	1.197	.3
	24 hours	393x10 ³	381x10 ³	<1	>.3
<i>S. paratyphi C</i>					
strain 1	8 hours	602x10 ³	415x10 ³	3.213	.02
	24 hours	401x10 ³	402x10 ³	<1	>.3
strain 2	8 hours	347x10 ³	268x10 ³	1.939	.1
	24 hours	328x10 ³	316x10 ³	<1	>.3

IN VIVO EXPERIMENTS

Groups of 24 mice each were inoculated with 10,000 ± 317 organisms belonging to the "V" and "W" types, respectively, of each strain. Of these 24 mice, 12 were killed after 8, and the rest of them after 24 hours. 0.1 cc. of the heart blood was diluted with saline and the number of organisms in the suspensions evaluated with the aid of the plate count. Four such experiments were carried out with each strain. The results were evaluated with the aid of the "t" test and are reproduced in Table No. II. This table shows that organisms containing the Vi factor multiply faster during the first period after inoculation than those without the Vi antigen.

TABLE II
MULTIPLICATION OF SALMONELLAE WITH VI ANTIGEN IN VIVO

Salmonella	No. of organisms in mouse blood from culture Vi form	O form	t	P approx.
<i>S. typhosa</i>				
Watson	172	98	>4	<.01
Bhatnagar	203	67	>4	.01
strain 3	101	62	>4	<.01
strain 4	98	42	>4	<.01
strain 5	41	30	2.678	.04
<i>S. paratyphi C</i>				
strain 1	157	104	3.124	.02
strain 2	72	21	>4	<.01

DISCUSSION

The survey of the literature showed that the Vi

factor plays an important role in the immunology of typhoid fever. While it was known that organisms possessing this antigen are more pathogenic for man and animals, the mode of their action was not elucidated experimentally as yet. The use of the technic of Bhatnagar permitted the isolation of pure "V" (Vi) and "W" (O) types from five strains of *S. typhosa* and two strains of *S. paratyphi C*. The statistical evaluation of the growth curves of these pure types in vitro and in vivo showed that there is a significant difference between the initial multiplication rates of the organisms endowed with the Vi factor and of the microbes derived from the same strain but deprived of the Vi antigen. It may be expected that typhoid bacilli and other Salmonellae containing the Vi antigen multiply faster, not only in artificial culture media and in experimental animals, but also in man, than microbes of the same species which do not possess this factor. It is known that organisms isolated during the first days of salmonellosis contain the Vi antigen more often (if the infection is caused by a Salmonella type which may have the Vi factor) than during later stages of the disease. It was observed in several instances that *S. typhosa* first lost its Vi antigen, then became rough during medication with antibiotics or sulfa drugs, while Salmonellae which never show the Vi antigen (as *S. typhi-murium*, *S. bareilly*, *S. montevideo*, etc.) become rough before they disappear from the blood or stool of the infected person (Felsenfeld and Young, 22). Thus, the regression follows the line: V — W — R.

The clinical importance of typhoid bacilli with the Vi factor is well illustrated by the observation of Goodall (23) who described an infection caused by a pure Vi form of *E. typhosa*. The patient died of septicemia and meningitis, without intestinal lesions. The greater invasiveness of typhoid bacilli with the Vi factor demonstrated itself in this case by the production of a rapidly fatal course, while, e.g., laboratory infections with old, W or R strains, rarely lead to such an end. It was proven that immunization against the "W" form alone does not protect against typhoid infection (Almon, 7). Neither does vaccination solely with the Vi antigen prevent typhoid fever. Immunization against both the Vi factor and the other antigens of typhoid bacilli, however, confers a fairly high degree of resistance (14, 21).

Difficulties encountered in the immunization against typhoid fever are similar to those met in the immunization against other enteric infections, e.g., *Sh. dysenteriae*, *V. cholerae*. While parenteral injections of the proper antigens cause the increase of specific circulating antibodies, the development of pathologic changes in the intestines is not wholly prevented by such vaccination. It is hoped that further studies of the local immunologic processes in the intestines, especially the clarification of the role of lymphocytes, will serve as a guide in the search for new ways of immunization against enteric infections.

After the disappointment caused by the failure of the sulfa drugs and streptomycin in typhoid fever, many physicians will probably resort to the simultaneous use of anti-Vi and anti-O typhoid serum. The

rapid initial multiplication of the typhoid bacilli with Vi antigen, however, calls for the injection of such sera at the earliest moment. Due to the insidious beginning of the classic typhoid fever, this requirement is difficult to fulfill. Sporadic cases, chiefly in immunized persons, are difficult to diagnose and specific therapy comes too late. The use of serum, therefore, remains restricted to epidemics and to highly endemic areas.

The rather late formation of Vi agglutinating antibodies in the sera of patients is similar to the failure of early agglutination tests in cholera. In both types of bacterial invasion the causative micro-organisms show a rapid initial multiplication. The work of Henderson and Morgan (24) and Topley et al. (25) led

to the belief that the biochemical composition of the Vi antigen, characterized by a specific polysaccharide, is such that other tests than the commonly used agglutination will perhaps render more useful results.

SUMMARY

The characteristics of the Vi antigen present in typhoid bacilli and other *Salmonellae* was discussed. Vi agglutination experiments failed to produce better results than other diagnostic means. Inoculation with Vi vaccines increased mouse protecting antibodies to a fairly high level. Experiments were carried out in vitro and in mice which showed that typhoid and paratyphoid C bacilli with Vi antigen show a stronger initial multiplication than organisms without the Vi factor. The importance of these findings is discussed.

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The Pathophysiology of Diabetes Mellitus*

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GENERAL CONSIDERATIONS

Diabetes mellitus is a clinical syndrome characterized by absolute or relative insulin deficiency, the etiology of which is as yet unknown for the human species. Literally, the term means "sweet polyuria," and until recently was considered to be due to lesions in the islets of Langerhans resulting in lowered insulin output. Heredity has a definite role in this disease, particularly in cases occurring in the first two decades in life, and the knowledge of this is one

of the chief weapons used in the preventive aspects of diabetes. Today, controversy over etiology persists but a broader concept includes any disturbance in the normal balance of regulatory factors, notably the pituitary, thyroid, adrenal cortex, and liver, which will result in the symptom complex.

The incidence of the disease appears to be on a definite increase. In early 1942 the National Health Survey placed the total number of cases at over 600,000 in the United States alone. Joslin (1) estimates that by 1950 the number is likely to reach a million. The disease is more common in the female, and appears to be more frequent in married than in single women. There is an increased incidence in both the Jewish and Irish races.

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There is also a high rate in individuals suffering from other endocrinological disorders such as hyperthyroidism (2) and acromegalia (3).

Onset of diabetes can occur at any age (cases recorded from two months to onset in one individual over ninety years of age), but it is most common between the ages of forty and sixty years. Diabetes developing after the age of sixty usually runs a milder course. At the present time the disease will on the average last twenty years due to improved therapeutic measures. It is, therefore, the diabetic child who poses one of the greatest problems to modern medicine since he must live so long with his disease. Obesity appears to be one of the most predisposing factors to the development of diabetes, especially in those cases which have their onset from the third decade onward. It has been found that gain in weight in experimentally induced pituitary diabetes in animals is, however, a part of the expected syndrome, but whether this has any significance regarding human diabetes is not certain.

The outstanding manifestations clinically of the uncomplicated case are characterized by insidious onset (especially in adults), with polyuria, polydipsia and loss of strength. Polyphagia, loss of weight and skin symptoms are also common. Diabetic neuropathy may occur early and almost invariably starts during a period of uncontrolled diabetes (4, 5). This is manifest as muscular cramps and aches, numbness, tingling and paresthesias, especially in the lower extremity, absent or diminished tendon reflexes (which Rundles states is the most valuable single diagnostic sign), genito-urinary and sphincter disturbances, and autonomic abnormalities including sweating, loss of vasomotor and pilomotor control, and dependent edema. When retinopathy occurs (usually in cases of long duration), it is commonly bilateral with characteristic ophthalmoscopic appearances. The susceptibility of the diabetic to arteriosclerosis and to infection, especially pulmonary tuberculosis and infections of the skin and urinary tract has long been recognized. The latter should be recalled in instances where catheterization during coma or after operation is necessary. It is arteriosclerosis which is today the chief cause of death in diabetes. Cancer of the pancreas, though relatively rare, has an incidence among diabetics with cancer that is two or three times as high as among non-diabetics.

The most important laboratory findings in the uncomplicated case include a persistent hyperglycemia, glycosuria, and a decreased glucose tolerance. Each of these may be found in disorders other than diabetes and careful interpretation of data must be made. In spite of this, the rule to consider all cases of glycosuria to be diabetic until proven otherwise appears to be well founded. Miller and Mason (6) report a series of sixty-four adult diabetics of all ages with varying degrees of severity, but in otherwise good health, fifty-eight of whom had a twenty-four hour urinary excretion of 17-keto steroids below the average normal level, and twenty-seven of these with values below the minimal normal level. It is evident that from such a series no definite conclusions can be drawn and that larger series must be carefully evaluated in order to confirm what might turn out to be a significant laboratory finding.

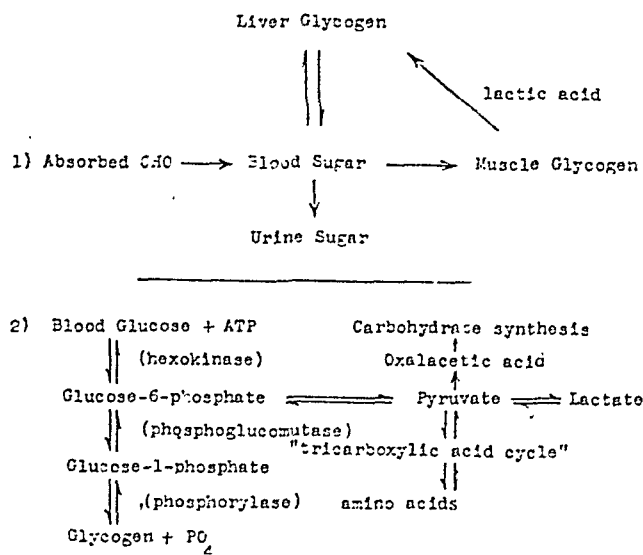
Seventeen years ago Boeck and Yater (7) reported elevated plasma carotene levels and low vitamin A levels in more than 85% of their large series of diabetics, but in a recent survey of 112 and 34 adult patients, Mosenenthal and Loughlin (8) failed to confirm such a finding. Nevertheless, one group (9) reports biophotometric evidence of A-deficiency in diabetes, and in the study it was found that even though the plasma carotene levels were normal the addition of more carotene failed to give a normal A content while added A gave normal biophotometric results. The crux of this discrepancy appears to lie in an inability of the diabetic liver to convert carotene to vitamin A. Another laboratory finding of questionable value is the elevated spinal fluid protein found in some cases of diabetic neuropathy by Rudy (10), but he states that this is not constant. In the elderly

diabetic the renal threshold for glucose is reported to be elevated (11), but this is not true in the young diabetic.

Clinically, the state of acidosis is ushered in slowly by a prodrome consisting of headache, anorexia, nausea, vomiting, painful, rapid respirations, acetone odor on the breath, cutaneous flush, and restlessness. Kussmaul respirations, gastrointestinal symptoms, dehydration, signs of circulatory failure, softening of the eyeballs and stupor indicate a severe state. At this time there is a low CO_2 combining power of the blood, ketonemia, ketonuria (which may, however, be absent in advanced stages if renal failure sets in), body demineralization, lowering of blood sodium and chloride, and a depletion of liver and muscle glycogen. If death should occur at this time, no specific organic lesions are found other than acute degenerative changes in cells of various parts of the central nervous system and cerebral capillary dilatation.

PATHOLOGICAL PHYSIOLOGY

The most important physiological mechanisms in the normal and in the diabetic are schematically represented below with a pertinent discussion of their main features with regard to the symptoms and signs described for the clinical state. The possible discrepancy in transferring results obtained in vitro or in experimentally induced animal diabetes to the disease in the human must be considered throughout these discussions.



Each of the three enzymes listed above in brackets beside the reactions they catalyze has been isolated and prepared in crystalline form. The current belief is that insulin functions in the step one conversion of glucose to glucose-6-phosphate, by accelerating in some manner this reaction, or by neutralizing some normally present inhibiting substance (12, 13, 14). It also seems probable that it is at this point that the diabetogenic element of anterior pituitary extract manifests its inhibiting action (12).

Stetten and Klein (15) recently demonstrated by the use of isotopes (deuterium oxide) that glucose given orally is to a large extent converted directly to glycogen without passing through a C_3 stage. They also found evidence to support the hypothesis that blood lactate (derived from muscle glycogen) is converted to liver glycogen. It has been shown by the use of isotopic carbon in CO_2 (16, 17) that the deposition of glycogen in the liver is accompanied by fixation of

CO₂. In order to explain this, it is necessary to assume that part of the glucose residues in glycogen is formed from C₃-C₁ or C₂-C₁ addition products. There is, however, no evidence to indicate that the latter reaction occurs in animal tissue. The former has been demonstrated in the conversion of pyruvate (C₃) + CO₂ to oxaloacetate, with this compound being in turn converted to phosphopyruvate and assuming a place in the metabolic cycle.

Other enzyme systems functioning in the reversible conversion of glucose-6-phosphate to 2-phosphopyruvate have been identified, and some of them isolated and prepared in crystalline form. These enzymes include phosphohexose isomerase (18), phosphohexokinase (19), aldose (20), isomerase (21), phosphoglyceraldehyde dehydrogenase (22), phosphoglyceromutase (23), and enolase (24), and these come into function in the order listed. For the breakdown of the energy-rich 2-phosphopyruvate to pyruvate, ADP or AA, as well as magnesium or potassium ions, are required. This reaction was until recently considered to be irreversible, but two groups of investigators (25, 26) have shown that it is reversible if the necessary constituents are present. Lactic dehydrogenase, an enzyme requiring the presence of DPN, has also been identified (27), and serves to govern the equilibrium between pyruvate and lactate. Adenosinetriphosphatase, the enzyme which prepares ATP for its transfer of PO₄ to glucose, fructose or creatine, has never been successfully separated from myosin, the protein in muscle responsible for its elastic and contractile properties. This close relationship (or identity) appears to be of considerable physiological importance.

The tricarboxylic acid cycle (28, 29) is the subject of a great deal of present day experimentation, and may assume a significance far beyond its function in carbohydrate breakdown. The possibility of amino acids and fatty acids being transformed into members of this cycle will be discussed, and it appears that this may turn out to be the final common pathway for carbohydrate, protein and fat metabolism, as well as a locus for interconversions between the three food-stuffs.

Englehardt and Barchash (30) were among the first to advance another possible pathway for carbohydrate metabolism, the "hexose monophosphate shunt." This consists in the direct oxidation of glucose-6-phosphate to phosphogluconic acid by means of the enzyme hexomonomophosphate dehydrogenase. Warburg and co-workers (31) have demonstrated that this can occur in animal tissue. It is believed that the blocking of anaerobic glycolysis (i.e., glucose-6-phosphate through pyruvate) by redox dyes or by oxygen is due to the sensitivity of phosphohexokinase (fructose-6-phosphate to fructose diphosphate). The significance of this reaction in the normal human and in diabetics is not clear as yet.

It has also been suggested (32) that in a liver damaged by toxins the normal barriers or environmental substance inhibiting amylase activity are disturbed and breakdown of glycogen to glucose by way of dextrin and maltose may occur. Insulin has no

place in this breakdown, and this may help to explain certain cases of diabetes with liver disease which are resistant to insulin therapy.

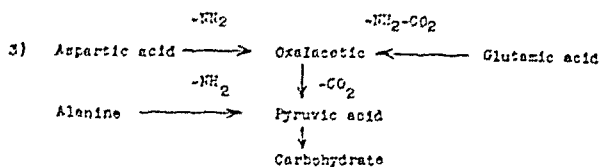


Fig. 1 — Only definitely proven amino acid conversions to carbohydrate (33).

A recent survey of the literature by Soskin (33) shows that there are actually only six amino acids which have been investigated thoroughly, i.e., by organ perfusion or in vitro experiments, regarding their conversion to carbohydrate, although many others have been implied to have a role through indirect evidence. Three of the six, namely alanine (34, 35), aspartic acid (36), and glutamic acid (37), will yield carbohydrate in definite proportions. Leucine, phenylalanine and tyrosine have also been shown to be convertible to their corresponding keto acids (38, 39), and it appears probable that these substances can in turn be converted to carbohydrate by entering into the tricarboxylic acid cycle. Green and co-workers (40) have prepared an L-amino oxidase from rat liver and kidney which catalyzes the oxidative deamination of several naturally occurring amino acids to corresponding keto acids. It should be pointed out here that about 45% of the casein molecule is composed of amino acids which may yield the keto acids common to carbohydrate metabolism.

This problem of gluconeogenesis from protein is of basic importance not only in nutritional work but also in the understanding of the nature of abnormal metabolic changes in diabetes mellitus. It appears that the inability of the diabetic organism to utilize carbohydrate at a normal rate is undisputable, but that there is evidence also of possible gluconeogenesis from protein which further disturbs the already unbalanced system.

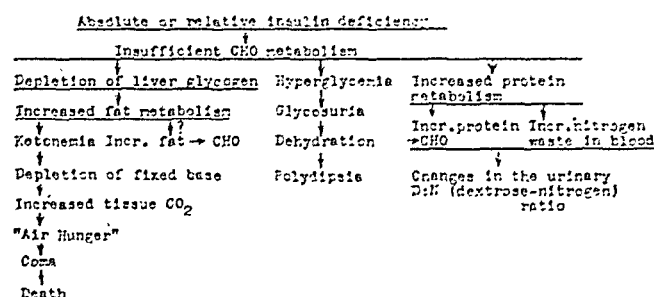
GLUCONEOGENESIS FROM FAT

The question of whether gluconeogenesis can occur from fat has remained unsolved for many years. The conclusions of Stadie (41) in 1942, after extensive experimentation, were that it can not occur. His findings have been confirmed by the recent work of Buchanan and co-workers (42) who, although they did demonstrate that acetate can enter the tricarboxylic acid cycle, feel that their experiments with isotopic carbon do not support the view that extra carbohydrate is formed during the metabolism of fatty acid. These men are strongly contested by Soskin who cites the work of Weil-Malherbe (43), Hastings et al. (44), and Rittenberg and Bloch (45), who demonstrated the incorporation of fatty acid carbon in liver glycogen and in amino acids. However, it should be noted that the isotopic carbons of the fatty acids were all in the carboxyl group, and the interchange of this carbon in metabolic processes probably represents simple redistribution and in this sense all three food-stuffs are interconvertible. There has not, however,

been any definite demonstration of fat yielding carbohydrate either in the normal or diabetic. Whether this will be shown in the future remains a matter of speculation and proposes a definite challenge to scientific investigation.

Another interesting aspect of this problem arose from the demonstration by Wieland and Rosenthal in 1941 that aerobic formation of citric acid could occur from oxaloacetic acid and acetoacetic acid in kidney and heart tissue. Using this mechanism Breusch (46) has proposed oxalacetic as becoming the meeting place between fat and carbohydrate oxidation, either directly by interchange of molecules or indirectly by competition in the reception of $-\text{CH}_2\text{COOH}$ from fatty acids (to form citrates) or $-\text{H}$ from sugar derivatives (to form malate). The preferential oxidation of carbohydrate is therefore regulated by the presence of a lower concentration of oxalacetic necessary for reduction by "sugar hydrogen" than the higher concentration necessary for condensation with keto acids. A relative absence of carbohydrate oxidation (as in diabetes) will therefore lead to decreased concentration of pyruvate and consequently oxaloacetate, and in so doing would allow for the accumulation of keto acids, i.e., diabetic ketonemia.

In the untreated diabetic the course of abnormal metabolic changes are thus:



KETONEMIA

a) Of the three substances grouped under the term "ketone bodies," namely, acetoacetic acid, β -hydroxybutyric acid and acetone, the second is not a ketone, and the third represents a breakdown of its more physiological precursors. It is now generally agreed that acetoacetic acid is the first ketone body to be formed. In the living animal the liver is practically the sole source of ketone bodies. Their fate in the normal is still somewhat obscure although it is recognized that these substances can be readily metabolized in a variety of peripheral tissues (47, 48). However, there appears to be a top rate at which muscle can utilize them and when this is exceeded by excessive production in severe diabetes, ketonemia results.

b) Carbohydrate ingested excessively does not tend to the development of ketogenesis. Glucose alone is antiketogenic, and combined with insulin is even more so. Glucose and insulin are not ketolytic. Their antiketogenic nature may be on the basis of both carbohydrate and fat having an affinity for the same enzyme systems, with the former having an inherent preference, or on the basis of Breusch's hypothesis (already mentioned). The chief danger on a physio-

logical basis of high carbohydrate ingestion in the diabetic lies in the polyuria and body dehydration that is produced, and in the possible exhaustion of what normal pancreatic tissue may remain.

DEPLETION OF FIXED BASE

Excess ketone bodies in the urine tend to draw organic acids and sodium from the blood stream, leading to a depletion of extracellular base. The resulting low base is inadequate to carry the normal amount of CO_2 from tissue to the lungs, so that the accumulation of CO_2 leads to a stimulation of the respiratory center with the typical "air hunger" developing. In addition, aceto-acetic acid is a powerful respiratory stimulant and may contribute to the dyspnea. Vomiting at this time is common and further leads to plasma electrolytic balance disturbances with depletion of plasma chloride. Experimentally in frogs depletion of electrolyte and glucose in the blood has been shown through electroencephalogram tracings to produce changes in the pattern of spontaneous activity (49), and this has been ascribed by Happenstall (50) to be due to changes of synaptic excitability.

POLYDIPSIA

This condition results from the excessive glycosuria since glucose excreted in the urine tends to draw water along with it (a physical principle) and body dehydration results. This leads to excessive thirst on the part of the patient.

MUSCULAR WEAKNESS

It is now known that more energy is derivable from a certain amount of glycogen (through pyruvate) than from an equivalent amount of blood sugar. It is probable, therefore, that the low levels of muscle glycogen in the diabetic are poorly utilized by him as a result of insulin deficiency and further complicates the procedure whereby the muscle can receive the energy necessary for the performance of work. In human diabetics the psychological element must be considered in this symptom. In spite of this, the appearance of weakness in a diabetic who has not been weak before, or an increase in one who has, is a characteristic and early symptom of acid intoxication.

URINARY GLUCOSE

Glycosuria occurs when the quantity of glucose delivered into the renal tubules in the glomerular filtrate exceeds the capacity of the tubules to reabsorb. The quantity of glucose filtered is a function of both glomerular filtration rate and plasma glucose level. In the young diabetic both the glomerular filtration rate and the glucose tubular reabsorption capacity are within normal limits. Therefore the plasma concentration level at which glucose first appears in the urine (renal threshold) is the same as that in the normal individual. In the elderly diabetic the renal threshold is commonly elevated (51), not as a result of any marked alteration in the capacity of the tubules to reabsorb, but because of the characteristic decrease in filtration rate. Only recently has this pathological depression been recognized and its cause determined (52). In the elderly

diabetic deposits of dense hyaline material are commonly found within the glomeruli between the capillary loops. All or most of the glomeruli are involved in some degree, and a few to the extent of almost complete obliteration. This condition, termed intercapillary glomerular sclerosis, increases in age with diabetes. It is occasionally seen in senile non-diabetics.

DIABETIC RETINOPATHY

This condition is a complication of prolonged diabetes and once it appears is not affected by the institution of insulin therapy. The changes are usually bilateral though not necessarily of the same degree in both eyes, and are characterized by small round deep-seated retinal hemorrhages and discrete white deposits in the retina which later become yellow and glazed. The number and arrangement of such lesions varies from a few of each scattered throughout the central areas to rather large masses of deposits which tend to involve the macular area. These changes do not depend upon either arteriosclerosis or hypertension though such conditions may be present in any one patient.

The pathophysiology of such changes is not as yet certain. However there is definite evidence (54) that certain processes are responsible. These include thrombosis of the retinal veins and capillaries. If the arterial limb of the capillary loop is occluded distal necrosis may occur. This may be the mechanism of the production of the above described white deposits. Experimental work is now being carried out in several institutions regarding the role of increased capillary fragility in the production of retinal hemorrhages. Gifford (55) summarized the evidence in favor of capillary fragility being responsible and though this is rather convincing no explanation is offered as to what causes the increased fragility of these vessels.

A less common but important complication is termed retinitis proliferans, which nearly always leads to complete blindness. In this condition large pre-retinal hemorrhage into the vitreous occurs. This is followed by the growth of new vessels into the veils of connective tissue left by incomplete absorption of such hemorrhage.

Clinically, diabetic retinopathy progresses slowly with long stationary periods. The end result, if the patient were to live long enough, is fibrosis and contracture of the retina with its subsequent detachment from the underlying choroid, producing complete blindness. In view of this the problem of diabetes in children becomes more acute to those who assume the responsibility for the treatment of such patients.

OTHER EYE MANIFESTATIONS

Among the most common eye signs produced by diabetes are changes in refraction especially in the older age groups. These are characterized by either sudden decrease in visual acuity or by repeated smaller changes in vision over comparatively short periods of time which necessitate unusually frequent refraction and change of glasses. The mechanism for such phenomena is understood and consists in changes in sugar concentration of the aqueous fluid of the anterior eye

which is in direct equilibrium with the circulating blood sugar. Such elevations or depressions of sugar content correspondingly change the refractive index of this fluid medium.

True diabetic subcapsular cataract, which is pathognomonic of diabetes mellitus, is relatively uncommon. These tend to be bilateral and occur preferentially in young individuals, running a more rapid course than the ordinary senile cataract. The pathophysiology is only partially understood but appears to lie in faulty metabolism of the actively growing lens tissue in the subcapsular lens area. No such characteristic changes occur in the more inert nuclear tissue.

The debated problem as to whether there is a greater incidence of the ordinary senile cataract in diabetes is as yet unsolved and discussion of such is beyond the scope of this paper.

DIABETIC NEUROPATHY

An interesting suggestion in this connection comes from the work of Mann and Quastel (53) who showed that pyruvate catabolism was necessary for the synthesis of acetylcholine in brain tissue. It appears that reactions involved in the oxidation of pyruvate are utilized to form the ATP involved directly in the synthesis of acetylcholine. In addition, there is evidence that pyruvate is a primary source of acetyl groups for the acetylation of choline. Since the role of acetylcholine in neuro-muscular physiology is such an important one, the possibility of explaining diabetic neuropathy on the basis of the above findings should be considered and investigated further in spite of the fact that there is no direct evidence to assume such to be the case.

In the experience of Rundles (5) with 125 cases of diabetic neuropathy, no vitamin deficiencies were noted, and the use of these substances therapeutically was without effect. He further states that he has never seen any clinical improvement by any treatment regime in the absence of effective diabetic control. It seems that the signs and symptoms are primarily reversible and only later progress to irreversibility when the patient is not controlled over a sufficient period of time.

The pathological features in cases of disturbed sensory function are described by Wofstman and Wilder (56) as being predominantly due to a vascular lesion of peripheral nerves with patchy areas of degeneration, more marked in the distal part of the peripheral nerves, together with an obliterating arteriosclerosis of the nutrient vessels. It would seem that this ischemia working in the face of disordered diabetic metabolism are sufficient to explain the sensory and motor phenomena.

ROLE OF THE PITUITARY

It has been shown that in cases of pituitary dysfunction glycosuria and true diabetes have an unusually high incidence. It was the work of Houssay that demonstrated conclusively that in previously hypophysectomized animals the diabetes produced by removal of the pancreas was extremely mild (57, 58). The injection of anterior pituitary extracts caused a

return of the usual diabetic state. It has also been found that permanent diabetes can be induced by the injection of anterior pituitary extract over a considerable period of time (59, 60, 61, 62, 63). From the experiments of Keller et al. (64) it is concluded that the pars tuberalis is probably the crucial tissue concerned with the elaboration of the hormone involved in these effects. It is of interest to note that the same extract used to produce pituitary diabetes in animals was injected into two patients who had pancreatic islet cell adenomas (65), but instead of producing the expected alleviating effects, further lowered the blood sugar levels. After treatment for twenty days the injections were discontinued and the blood levels rose to, or slightly above, pretreatment values. It is difficult to interpret this, but the authors (65) believe it to be an expression of the presence of an insulintropic substance which manifested itself in an already hyperfunctioning gland.

In attempting to localize the action of APE in producing experimental diabetes, the premise has been advanced that the site of inhibition is in the conversion of glucose to glucose-6-phosphate, either directly on the reaction or indirectly by inhibiting the action of hexokinase. There does not seem to be any direct evidence of action of APE on the pancreas per se (66). Apparently there is a definite antagonism between insulin and APE for the effects of the latter are abolished by the presence of adequate amounts of insulin both in vivo and in vitro.

THE ADRENAL GLANDS

The influence of these glands on carbohydrate metabolism was thought for a long time to be due solely to the secretion of the medulla, but today the concept is changing and the cortex is assuming a far more important role. In fact, the work of Vogt (67) showed that epinephrin given in physiological doses caused an immediate and long lasting output of cortical hormones. In view of this, it seems possible that the decreased blood sugar utilization after epinephrin injection may be due entirely to increased steroid secretion.

The chief problem now in understanding the mode of action of the cortical hormones lies in discovering whether they tend to decrease peripheral utilization of carbohydrate or whether they function only to stimulate gluconeogenesis, as Soskin professes. It is his belief that the latter occurs through increased mobilization and catabolism of both protein and fat, though he is well contested in this assertion. Recent reports by Doetsch (68) and by Montigel (69) are indicative of decreased glycogen phosphorylation in tissues of adrenalectomized rats, which was brought back to normal by administration of cortical hormone. Similarly, Olsen found that simultaneous administration of corticosterone and 17-hydroxycorticosterone was ineffectual. It is apparent that there is a wide discrepancy between the conclusions drawn by the latter three authors and those expressed by Soskin. The complete answer is not available at this time, and certainly offers a perplexing problem to the investigator.

THE THYROID GLAND

Houssay (70) has presented data of interest on the relationship of thyroid activity to diabetes. He found, as others have, that thyroidectomy does not appreciably alleviate pancreatic diabetes in dogs, nor does the administration of thyroid hormone to normal dogs or rats produce diabetes. However, partially depancreatized dogs that were not actually diabetic, were quite sensitive to thyroid hormone, for treatment with it would produce a temporary or permanent type of diabetes. Also the diabetes of completely depancreatized dogs was made more severe by giving thyroid. It would appear that hyperthyroidism would lead to an increased need for insulin, and this may consequently lead to an exhaustion of an already damaged pancreas. Therefore, it may be concluded that thyroid may possibly be a factor in the production of the permanent type of pituitary diabetes from an overstimulation of the gland by APE.

The transference of this experimental data to the human is filled with hazards. However, there is an increased incidence of diabetes in individuals suffering from hyperthyroidism, and it may be that the thyroid is the precipitating agent in a predisposed individual.

THE SEX HORMONES

Administration of sex hormones in large doses is known to exert a suppressive action upon the gonadotrophic hormone of the anterior pituitary, and possibly upon the diabetogenic element (61, 70, 71, 72, 73), though the latter action is at present little understood. Evidence has been presented to show that diabetes which has its onset related in some way to the menopause, is favorably affected by estrogens in sufficiently large doses (72, 74). This finding was not found to be true in patients whose diabetes had no relation to the menopause. Young (74) was unable to demonstrate any beneficial effects from estrogen treatment in pituitary diabetes in laboratory animals.

INFLUENCE OF THE LIVER

Abnormal glucose-tolerance curves have been demonstrated in patients suffering from acute infectious diseases. Soskin and co-workers (75) have ascribed this change as being due to a toxic effect on the liver, interfering with its regulatory mechanisms in carbohydrate metabolism. There is also direct in vitro evidence of the influence of toxins on this regulatory mechanism (76). In cases of advanced liver disease the abnormal curve appears along with other signs of grossly abnormal liver function.

The progressive effects, demonstrated on liver slices by Holmes (76) and arranged in order of sequence, are described as being first, an increased rate of glycogenolysis, and second, a decreased ability to convert the three-carbon compounds into glucose (more or less complete inability to form liver glycogen).

Of possible clinical value in differentiating the effects of hepatic from endocrine dysfunction as a basis for an abnormal tolerance curve, are the experiments of Soskin (77). His results indicate that by using a standardized intravenous procedure for the glucose-

tolerance test, a normal, hepatic and endocrine curve can be identified by the downward slope of the curve and by the time that it takes to return to the preinjection level. It is apparent that a larger series from other clinics must confirm this finding before it can be definitely accepted.

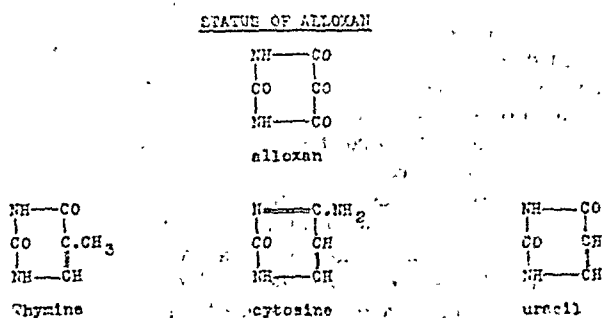


Fig. 2 — Structure of alloxan, showing its close relationship to certain derivatives of naturally occurring nucleoproteins. Possibility that alloxan, or some similar substance arising from a disordered nucleoprotein metabolism, may have some bearing on the etiology of diabetes has been advanced (78).

At present the place of alloxan in the pathophysiology of diabetes cannot be stated with any degree of certainty. It has been demonstrated that this substance will definitely destroy the beta cells of the Islets of Langerhans, and Joslin feels that this fact is of great importance in the eventual explanation of diabetes. His opinion is strongly contended by Duff (66), who professes the belief that it is most improbable that alloxan plays any role in the etiology of human diabetes.

Nevertheless, there are resemblances between experimental diabetes produced over a period of weeks by small doses of alloxan and that produced by partial pancreatectomy or by anterior pituitary extract. In the former a wide variety of changes in the beta cells, including degeneration and hydropic degeneration, as well as completely normal cells are found. However, the alpha cells are not affected (80, 81), and the hypothesis has been advanced that these cells elaborate a separate hormone which increases blood sugar and yet prevents ketosis. It appears that the changes produced are at first reversible either per se, or by compensatory hyperplasia of unaffected elements, and only later progress to irreversible cellular damage.

Whether these pancreatic changes are due to direct action of alloxan is not certain but most of the available evidence points to this being the case. Its rapid destruction at the pH and temperature of the blood (half time is about four minutes) and its reactivity with thiol and other groups explain its almost complete disappearance from the blood five minutes after intravenous injection. According to several investigators, the main decomposition products of alloxan in the blood, alloxanic and dialuric acids, are not diabetogenic. It is therefore to be expected that damage to the islet tissue would occur in the first few minutes after injection, and this has been demonstrated (82) in dogs. Degenerative changes have also been described in the basophil cells of the pituitary and in the adrenal cortex following large doses of alloxan (83).

Houssay (84) concludes from his experiments that the liver plays an important role in alloxan diabetes: 1) In the primary phase direct action of alloxan on the liver results in increased gluconeogenesis and subsequent hyperglycemia; 2) There is a secondary hypoglycemia, not due to liberation of insulin, but rather due to lack of glucose production by the liver; 3) The final hyperglycemia is mainly due to destruction of the beta cells of the pancreas and becomes permanent in duration. Direct assay of the pancreas at this time shows greatly reduced insulin con-

tent. This investigator also noted that the final hyperglycemia is sometimes higher in alloxanized than in depancreatized dogs. Thorogood and Zimmerman (85), in turn, found the glycosuria to be more severe and the insulin requirement to be higher in alloxan diabetes, but found, however, that these dogs tended to survive longer without insulin and showed less ketonuria, and did not develop coma. Removal of the pancreas at this time reduced glycosuria and lowered insulin requirement, but when insulin was then removed (withheld), ketosis and coma developed rapidly. Their implication there was that the alpha cells do play a role in diabetes.

STATUS OF PHLORIDZIN*

This chemical (a bitter glucoside, shown by von Mering in 1886 to produce glucosuria in animals) was used extensively by Lusk and co-workers (86), and others, as a tool to study carbohydrate metabolism and fathom the mystery of diabetes. Following its parenteral administration there follows a continuous excretion of sugar in the urine, without preceding hyperglycemia.

There have been several theories advanced for its mechanism of action but none have proven entirely satisfactory. At first this phenomena was thought to be due to toxic effects on the kidney, thereby lowering the renal threshold. Recent work by Engelhardt and Lyubimova (87) indicates that phloridzin has a primary function of inhibiting the formation of ATP during reactions which liberate the energy-rich phosphate radical, i.e., it inhibits the action of adenosinetriphosphatase (ADP-ATP). Such a finding is in harmony with the fact that glucose absorption by the kidney is an aerobic process and requires ATP in the formation of absorbed hexose phosphate. This, however, still lies within the possibility stage and though it certainly seems logical, has not been definitely established as fact. There is no evidence in the available literature that phloridzin has any effect directly on the pancreas.

Much noteworthy work has been done in an attempt to establish a "phloridzin test" as a reliable clinical indicator of kidney function, but as yet none has been completely successful.

THE PANCREATIC HORMONE

There has been slow but steady progress made in discovering the physiology of insulin since its discovery by Banting and Best twenty-five years ago, but there is as yet much to be learned before its role is completely understood. It is clear that insulin exerts its influence on the rate of glycogen formation from glucose, but it is not essential for this conversion. In this way it is similar to other hormones in the body. This fundamental fact was verified mainly through the work of Gemmill (88, 89, 90), Cruickshank (91), Levine and Soskin (92), Shorr et al. (93, 94), Stadie (41) and Cori (95). According to Hechter, Levine and Soskin (96) insulin will further permit rates of carbohydrate utilization at low blood sugar levels which in its absence necessitates extremely high levels. They are, however, contested in this belief by several investigators who feel that glucose will not be utilized even with very high levels (97).

Swenson, in a recent cogent review, concludes that insulin brings about a reduction of the liver glycogen content. This applies to all dosages that have any effect at all. The decrease in liver glycogen in amount and duration is proportional to the dose. No increase was ever noted. The reduction always runs parallel with a reduction in the blood sugar. The glycogen content in the rest of the body, reckoned in percentage, is increased under the action of insulin, if doses are large. It seems most probable at the present time that these various physiological effects of insulin do not represent different and unrelated functions of the hormone, but instead are

* Also termed Phlorhizin, Phlorizin and Phlorrhizin. For a recent comprehensive review of the literature the reader is referred to McKee and Hawkins, *Physiological Reviews*, 25:255, 1945.

indirect consequences of a single catalytic influence upon a basic enzyme system. The locus of this influence has not been definitely established, but Cori (12) feels certain that as a result of his extensive experiments its action is on the step one conversion of glucose to glucose-6-phosphate, as described previously in this paper. As yet it cannot be said whether this stimulating action is due to direct acceleration of the enzyme system, or an inhibition-removing action of the hormone.

In favor of the latter are results of experiments by Price et al. (98, 99). They produced an *in vitro* inhibition of the hexokinase reaction by the addition of isoelectric protein fraction of anterior pituitary, which was greatly reinforced by adrenal cortex extract, and found that this inhibition could be removed by insulin. When no inhibition was present, no effect on the hexokinase reaction could be demonstrated with insulin. The conversion of glycogen to lactic acid in muscle extract was not inhibited by pituitary extract. It has also been discovered recently that chymotrypsin inactivates insulin *in vitro* but does not prevent its hypoglycemic effect when the two substances are injected simultaneously into rabbits and dogs. Intravenous injection of chymotrypsin alone has no significant effect upon the blood sugar of these animals (100).

Finally, in summing up the effects of insulin's catalytic power of rendering more substrate (glucose) available to the tissue enzyme systems in suitable form (glucose-6-phosphate), it is evident from biochemical principles that carbohydrate is allowed to become predominant over fat and protein in competition for the enzymes present. Hence, the mechanism of the "protein-sparing" and "antiketogenic" effects of carbohydrate and insulin can be understood.

SUMMARY

It has been the purpose of this paper to correlate the clinical characteristics of diabetes mellitus with the pathophysiology of the disease and to summarize some of the chief features of experimental diabetes as cited in the literature up to December, 1946. It is apparent that a great amount of material concerning the fundamental processes at fault has accumulated, but also that as yet much remains to be discovered before the disease entity will be completely understood.

One of the greatest difficulties at the present time lies in the interpretation of animal experimentation and the relation of experimental diabetes to the human form of the disease. Certain conclusions can, however, be drawn from the data presented:

1) It is no longer possible to think of the metabolism of the three basic foodstuffs — protein, fat and carbohydrate, in separate terms, for the mechanisms of all three are closely interrelated and have an influence upon one another.

2) It appears that the defect in diabetes is not localized in one organ, i.e., the pancreas, but instead may lie in, or be profoundly influenced by, inherent dysfunction of other organs, the pituitary, thyroid, adrenal cortex or liver. Nevertheless, it must be emphasized that none of these considerations minimize the importance of insulin as the therapeutic agent.

3) The role of heredity in this disease entity is of great importance, not only as an etiological consideration, but also as a strong weapon in preventive aspects.

4) The role of some diabetogenic chemical now seems a possibility. It is apparent, however, that further studies must be made with slowly-produced alloxan diabetes before any conclusions relevant to human diabetes can be drawn. The search must be continued with similar compounds to see if perhaps there may be some chemical substance that is responsible. It is of interest also that so far no agent has been discovered which will produce diabetes without definitely injuring the insulin producing cells. Perhaps some factor will be found which produces the condition of clinical diabetes without acting by way of such cellular impairment. If such an agent were active in humans it might be possible to counteract it in such an early stage that no permanent damage to the pancreas would be produced.

5) One of the most feared complications of diabetes and one that, once it appears, is little influenced by insulin therapy, is diabetic retinopathy. The incidence of such a complication appears to be on the increase and the pathological mechanisms at work deserve the cooperative study of internists and ophthalmologists alike.

6) Early diagnosis, diligent following of the patient by his doctor, education of the patient concerning the nature of his disease, and further research are the chief hopes of modern medicine in controlling this widespread disease.

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Adrenergic Potentiation, a Pharmacodynamic Effect Associated with Antihistaminic Agents

By

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SEVERAL NEW COMPOUNDS capable of nullifying certain pharmacodynamic actions of histamine and allergens have been announced in recent years: Antergan (1), Neoantergan (2), Benadryl (3), Pyribenzamine (4), Antistin (5), and Hetramine (6). Pyribenzamine, like others (1, 2, 3), also has analeptic, local anesthetic and adrenergic potentiation actions which were initially reported last year (7). The present paper extends the study of the last property.

RESULTS

The potentiation by Pyribenzamine of epinephrine's action in the cat has been reported (8) with respect to salivation, retraction of the nictitating membrane and elevation of blood pressure and these effects are illustrated in Figures 1 and 2. Potentiation of the effect of faradic stimulation of the feline cervical sympathetic nerves controlling salivation and retraction of

the nictitating membrane is also demonstrated in these figures and thus indicates that adrenergic and sympathetic actions of *varied* SE effector mechanisms are potentiated by Pyribenzamine. Adrenergic potentiation of epinephrine's relaxing effect through SI effector mechanisms associated with canine intestinal muscle is illustrated in Figure 3. In canine anaphylaxis (horse serum) Pyribenzamine almost invariably produced a moderate degree of hypertension (Table I), apparently as a result of adrenergic potentiation, and this feature will be presented in greater detail in a forthcoming paper dealing with certain vascular reactions to Pyribenzamine in normal and anaphylactic experimental subjects. The potentiation of epinephrine's vascular effects has been reported for other antihistaminics: Antergan (9), Benadryl (10, 11), and Neoantergan (2, 12).

DISCUSSION

In many of its actions histamine duplicates those characteristic of acetylcholine; it produces hypotension.

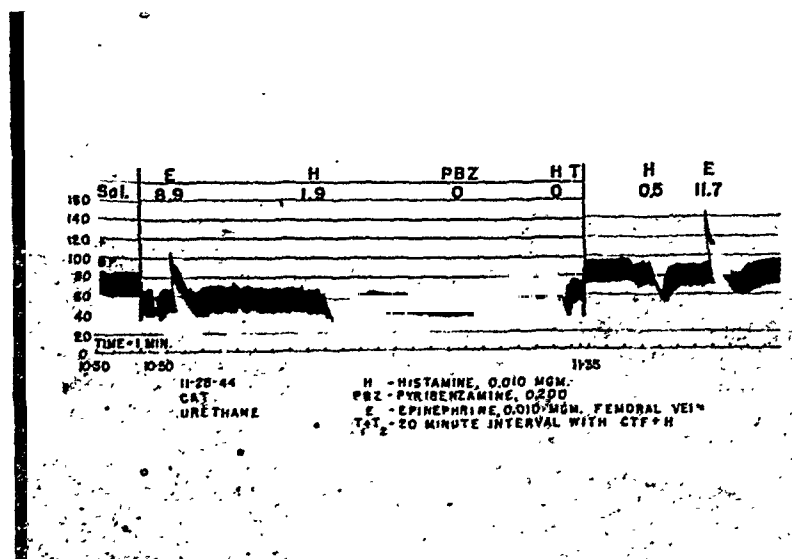


Figure 1 — 11/28/44, Cat, urethane anesthesia. Pyribenzamine 0.200 mg. elevated the blood pressure, nullified the action of histamine, 10 micrograms, on salivation, lessened the hypotensive effect of histamine and potentiated the vasopressor and calivary effects of epinephrine, 10 micrograms.

secretion, and contraction of smooth muscle. Actually there is definite evidence available substantiating the contention that histamine produces its effects through the mediation of acetylcholine (13, 14). Whereas atropine is a relatively weak antihistaminic but strong anticholinergic agent, most histamine antagonists are rather weakly anticholinergic but strongly antihistaminic; hence, their chief designation as such in the conventional but not entirely satisfactory system of classi-

fying pharmacologic agents. It is therefore not difficult to appreciate that after inhibition of such cholinergic stimulants as histamine or acetylcholine, as effected either by such antihistaminics as Benadryl or Pyribenzamine, or by such an anticholinergic agent as atropine, the functions of the unopposed sympathetic nervous system come into prominence, thus influencing the observer to attribute to such agents "sympathetic or adrenergic" potentiating properties. Whether this be

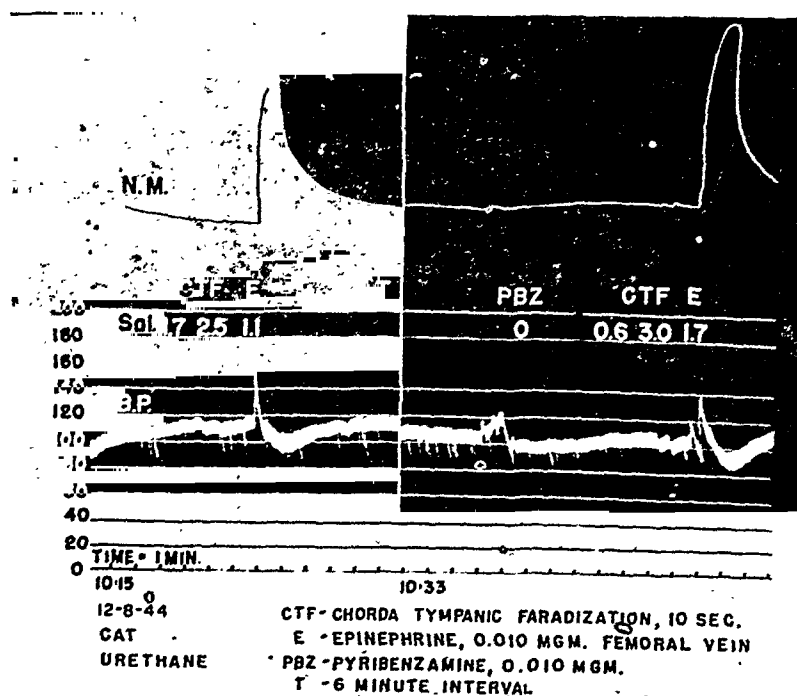


Figure 2 — 12/8/44, Cat, urethane anesthesia. Pyribenzamine, 0.010 mg. potentiated the effect of epinephrine, 10 micrograms, on the retraction of the nictitating membrane and on the induction of salivation.

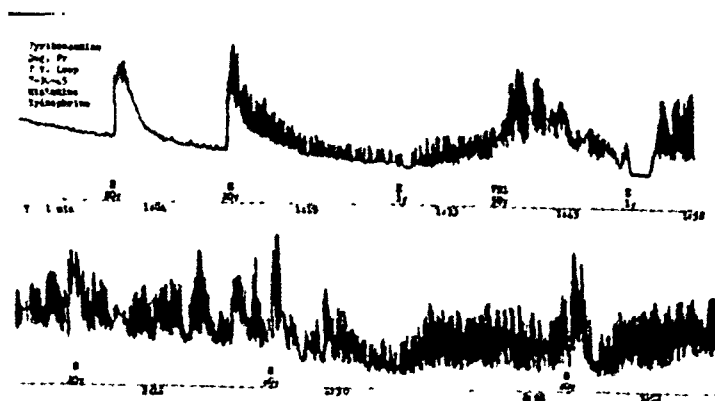


Figure 3 — 7/30/45, Dog, pentobarbital anesthesia, Thirty-Vella loop preparation. Pyribenzamine, 0.050 mg. increased intestinal tone and transiently potentiated the inhibitory effect of epinephrine, 1 microgram, on intestinal activity.

relative or true potentiation can probably be best determined by studies of enzymes associated with the normal breakdown of adrenergic stimulants; this work is now in progress.*

The concept that there is some counterbalancing relationship between histamine and epinephrine is strengthened by the work of Staub (15) which indicates that epinephrine conversely causes a prominent release of histamine in the body, probably as an antidote to many of the exaggerated actions of epinephrine. Such a protective mechanism is obviously lost in the presence of antihistaminic agents (including adequate dosage of atropine) thus permitting an enhancement of adrenergic and sympathetic responses.

The significance of adrenergic potentiation is obvious: if epinephrine or sympathin be spared under the influence of antihistaminic compounds, then the effect of nature's best physiologic agent for the control of many allergic symptoms is enhanced. Its prolonged effect thus might be due either to some disturbance of its enzymatic detoxification, or/and to the dampening by Pyribenzamine and similar agents of epinephrine's antagonist, histamine (Staub).

SUMMARY

An important pharmacodynamic action of certain compounds known as "antihistaminic agents" is that

* Since the completion of this manuscript we were privileged to read a manuscript prepared by Dr. E. Loew and his co-workers, which deals with this subject (12). These investigators observed potentiation of epinephrine's hypertensive action in atropinized dogs treated with Benadryl, Pyribenzamine, and Neoantergan. Their findings definitely established our own contention (7, 8) that adrenergic potentiation is a prominent pharmacodynamic action of antihistaminic agents.

TABLE I
Anaphylaxis - Pyribenzamine
Dog 4

Date	Procedure	Press.	Pulse	Resp.
11-6	Sensitized			
12-1	Normal	88	84	12
	Horse serum	32	120	42
3.5 mgm./kg., Pyribenzamine				
12-5	Normal	100	90	12
	Pyribenzamine	112	120	36
	Horse serum	131	168	12
12-9	Normal	92	120	36
	Horse serum	29	150	42
1 mgm./kg., Pyribenzamine				
12-14	Normal	110	180	24
	Pyribenzamine	110	150	12
	Horse serum	44	150	14
2 mgm./kg., Pyribenzamine				
12-18	Normal	78	126	13
	Pyribenzamine	97	120	42
	Horse serum	34	120	18
3.5 mgm./kg., Pyribenzamine				
12-30	Normal	86	120	10
	Pyribenzamine	102	114	24
	Horse serum	96	120	18

Table I, 12/5/44, Dog, sensitized to horse serum. Pyribenzamine, 2 to 3.5 mg., elevated blood pressure which was determined by arterial puncture under pentobarbital anesthesia.

of adrenergic potentiation. This feature has been demonstrated in reference to the adrenergic control of feline blood pressure, salivation and retraction of the nictitating membrane, and of canine blood pressure and intestinal motility.

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Histoplasmosis

By

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RECENTLY THERE HAS BEEN a renaissance of interest in histoplasmosis, primarily because a number of adults in certain areas of the United States seem to have passed through subclinical episodes of this disorder. Some of the details of this aspect of the problem, with its many epidemiologic facets, will be touched upon later.

The highlights of the early development of our knowledge of this disease may be briefly summarized. In 1906, Darling (1) reported the discovery of a disease in Panama, apparently similar to visceral leishmaniasis, and seemingly caused by protozoans readily seen in histologic sections. Not until twenty years later was a comparable case reported from the continental United States. In 1934, de Monbreun (2) successfully cultured the organism from the blood of an infant, and by demonstrating the mycelial forms, clearly proved it to be a fungus and not a protozoan. Later he was able to inoculate monkeys and mice. Puppies were infected by feeding the mycelial form. This fact is obviously of clinical importance because it demonstrates that the mycelia may survive exposure to the gastric juice and that the infection may enter the body via the gastro-intestinal tract. By 1939, only four cases had been reported in the United States, but one year later, Meleney (3) was able to collect 32 cases, plus 13 not previously published.

Histoplasmosis, as already stated, is caused by a fungus known as *Histoplasma capsulatum*. This fungus is unique in that it is the only one pathogenic for man which is primarily an intracellular parasite of the reticulo-endothelial system. The organisms may multiply within phagocytic cells that engulfed them.

In tissues this parasite appears as a round or oval body, 1 to 5 micron in cross section, with chromatin irregularly distributed at its center, and with a colorless, refractile capsule. Hematoxylin-eosin or, preferably, the Giemsa stains, will demonstrate the organism. The mycelial form appears on culture using blood-agar, or Sabouraud's medium, but it may require from three to four weeks, at room temperature, before growth appears (4).

As can be inferred, the organs most frequently involved are those with abundant reticulo-endothelial tissue. Thus, the lymph nodes, spleen, liver, bone marrow, and the lymphoid structures of the pharynx and gut are common sites of a relatively chronic granulomatous infection (5) and ulcerations of the skin, mouth, pharynx and bowel may occur. Only cartilage and the cortex of bone, being devoid of lymphoid tissue, invariably escape (4).

Grossly, grey-white nodules or ulcerations may be seen on the surface of the involved organs. Microscopically, there is proliferation of the lymphoid tissue with pronounced cellular destruction and the organisms may be seen within monocyctic cells which have phagocytosed them. Around this zone of necrosis is granulation tissue with macrophages containing the parasites. This extensive parasitization of cells of the reticulo-endothelial system results in hepato- and splenomegaly and lymphadenopathy, while the common infection of the marrow brings about the anemia and leukopenia characteristic of histoplasmosis.

The symptoms of histoplasmosis obviously may be exceedingly varied. In general, it appears as a systemic febrile disease associated with weight loss, anemia, leukopenia, and enlargement of the liver, spleen and lymph nodes. Gastro-intestinal disturbances, including diarrhea, occur in nearly two-thirds of all cases, while oral lesions, which may simulate those of leukemia, Hodgkin's disease, noma or carcinoma, were present in 20 per cent of 70 reported cases (6). Pulmonary

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spread, as verified by roentgenologic examination, is usually characterized by multiple small foci, frequently subpleural, but it seems that the lungs are more often secondary sites of infection rather than the portal of entry of the fungus (7). From these remarks it becomes evident that there is no "typical" clinical picture of histoplasmosis but that it may mimic many a systemic disease. Indeed, a case of endocarditis, due to *Histoplasma capsulatum*, has been reported (8).

Histoplasmosis has been observed in various races, approximately equally in both sexes, and without correlation with any occupation. One-fourth of a series of 48 cases involved children under the age of thirteen years. The duration of the disease varies from one to eight months, although a few adults have apparently resisted the infection for a few years. The outcome, in clinically recognized cases, is uniformly fatal (5).

The ultimate diagnosis of histoplasmosis rests upon laboratory evidence. The parasites may be seen in thick smears within the monocytes of the peripheral blood. Puncture of the spleen or sternal marrow may likewise reveal the organisms, as may biopsy of accessible sites of infection. Inoculation of guinea pigs with blood or an attempt to cultivate the parasites on suitable media may prove successful.

Treatment of clinical histoplasmosis has been uniformly unsuccessful. Pentavalent organic antimony compounds, neoarsphenamine, potassium iodide, and radiation therapy are of no evident value. Likewise sulfonamides, and in a few cases penicillin, have not altered the downhill course.

The only case of histoplasmosis on record at the University of California Hospital (9) is that of a 37 year old laborer who was first seen by us in 1943. His symptoms, namely, swelling of the left side of the neck, had appeared in 1937. The swelling spread gradually to his cervical, axillary and inguinal lymph nodes and was accompanied by loss of weight, intermittent fever, and weakness. A lymph node was removed in 1938 for biopsy and his illness, at that time, was diagnosed as Hodgkin's disease, for which he received Roentgen ray therapy to his chest, back and

inguinal regions. Finally he entered the University of California Hospital in 1943 with the same complaints and during examination an ulcer of the tongue was discovered. A scraping from this lesion revealed the presence of *Histoplasma capsulatum* on microscopic examination and when the previous biopsy of the lymph node was carefully checked, a single mononuclear cell was found, containing inclusions resembling the organisms seen in the ulcerated tongue. The patient was treated in the hospital with neostam, para-amino-benzoic acid and penicillin, but died in June 1944.

Perhaps the most intriguing feature of histoplasmosis is its epidemiology. There is evidence accumulating which suggests that this disease may have a benign form, analogous to the subclinical infection of coccidioidomycosis and tuberculosis (10). Skin tests with histoplasmin, which is simply a sterile broth filtrate of *Histoplasma capsulatum*, are positive in a significant number of individuals who give no history of evident infection. These investigations, pioneered by Dr. Amos Christie (11), were initiated because in routine mass chest surveys many persons were discovered with pulmonary calcifications who, however, were negative to tuberculin. In certain areas, as in California, coccidioidomycosis may be the cause of such calcifications. However, skin testing with histoplasmin has demonstrated that many react positively. At least in the southeastern United States, histoplasmosis seems to be the principal nontuberculous cause of pulmonary calcifications. Thus, in a survey of 3,105 student nurses (10), calcification was present in 31.1 per cent of those positive to histoplasmin, but in only 10.4 per cent of those positive to tuberculin.

The only disconcerting point about these data is that both experimentally and clinically, other fungi appear at times to produce a positive reaction to histoplasmin (12). However, the facts mentioned do open several avenues of investigation and in the immediate years much should be added to our knowledge of this disease. This will require alertness on the part of clinicians, radiologists, epidemiologists and pathologists.

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The Cell-Cleaning Therapy and the Liver Cell Gymnastics in Treatment of Chronic Hepatitis *

By

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THE TREATMENT about to be discussed has proved highly satisfactory during the last twelve years. It is based on the following facts and observations.

A dye for cholecystography (Tetraiodophenolphthalein) injected intravenously disappears from the blood within 30 to 40 minutes. The gall bladder becomes visible by x-ray as a rule, only after 14 hours following the injection, reaching a maximum density of shadow around the sixteenth hour. Where has the dye been in the meanwhile? The generally accepted answer is that the dye is excreted with the bile and present in the bladder within an hour after injection however, in a dilution below x-ray visibility. The dye-containing bile is then concentrated in the bladder five to eight times until, after some 15 hours, it reaches full x-ray density. This process of concentration undoubtedly takes place and causes the x-ray density to increase hourly. However, this explanation only partially covers what actually happens, as can be proved by another simple experiment. When following dye-injections, 20 cc. of a 50% glucose solution is injected, the gall bladder gives a shadow of sufficient density within two hours. This fact obviously challenges the correctness of the assumption that concentration-time of the bile fully explains delayed x-ray visibility.

The experiment can be amplified by injecting glucose at different intervals after the dye-injection. The shadow appears almost regularly one or two hours thereafter. That is to say, when a sudden great glucose amount is offered to the liver cell, it *cleans out the stores of other products to make space for the increase in its glycogen*. The following observation (F. C. Mann) supports this thesis: When injecting a larger amount of glucose solution into a dog, the glycogen in the liver increases by 20%. At the same time, the bilirubin level of the serum rises and bile may even appear in the urine. That means that the pigment stores are thrown out of the liver cells to make place for the glycogen. However, hypertony of the solution is essential. Solutions of 10% glycogen have practically no effect, thus indicating that electro-osmotic conditions also play a role.

A fundamental problem is whether the cell-cleaning effect of hypertonic glucose is extended to products of normal nutritional metabolism as well in a manner similar to that of these hepato-trop substances eligible to be excreted with the bile. Many observations suggest in fact that the *sudden introduction of concentrated glucose into the liver, induces the liver cells*

to dispose of other stores. Glycogen storing function is apparently one of the strongest vital functions of the liver cell, explaining why a complete glycogen-deficiency is found only in cases of extreme breakdown of the liver parenchyma. When this function is severely damaged, no amount of glucose can resupply the storing place and save the patient from hepatic coma.

If, however, the glycogen storing function is not entirely lost, a supply of concentrated glucose solution may change the entire chemical structure of the cells. It is fairly well established that when fat in larger amounts is stored in the liver cells, glycogen is greatly diminished, or, to put it in another and probably more correct way: a diminished glycogen-supply is replaced by fat which, in its uselessness for cell metabolism, may well be termed the "weed" of the cells. Formerly this fatty infiltration was considered a sign of serious cell-damage just short of actual death. It was thought to be an irreversible process. It is not. Liver-biopsy specimens obtained in cases of relaparotomy or by the punch-method have revealed that, under appropriate treatment, a cellular and structural recovery of the liver lobules may take place, fat deposits may diminish or even disappear, and increasing glycogen amounts become deposited in the cells.

Recent experiments with the so-called lipotropic substances — sulfamino acids (methionine), lecithin, Vitamin B complex and others — have similarly depleted fat deposits in the liver cells although by a different mechanism. These substances act presumably by forming intermediary conjugated products with fats so that they are brought back into the stream of active metabolism. The presence of labile methyl-groups in the substances apparently is essential to the lipotropic effect. Hypertonic glucose solutions, it would seem, work differently, osmotic conditions playing a role additional to the preferential place of glycogen in the cells.

An interesting case of hemosiderosis is briefly presented in order to demonstrate the cell-cleaning effect on hemosiderin.

CASE REPORT

Mrs. M. G., 62 years of age, gave the following history. As a girl she had always been anemic. Married at 24. Two abortions between the third and fourth months. In 1924 she was on a strict diet because of pain and discomfort in the liver. In 1933 she had a nervous shock (private affairs) followed by all sorts of nervous troubles. She felt some numbness in legs and fingers, suffered with cramps, and her gait gradually became unsteady. She consulted a nerve specialist who established the diagnosis of anemia and combined sclerosis. She received fresh liver, liver extract, and iron capsules (17 gr. nine times daily) from 1933 to 1940 with remarkable success. Her nervous ailment disappeared completely.

* A chapter from the book, "Hepato-Biliary Diseases," by B. O. C. Pribram, to be printed by Charles C. Thomas, Publishers, of Springfield, Illinois, in 1948.

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In 1942, considerable enlargement of the liver was noted for the first time, and she was under the care of several specialists. In 1944-45 she complained of increasing enlargement of her abdomen and pain in the liver. The liver was found to be greatly enlarged and hard. Laboratory findings at this time showed a slightly increased sedimentation rate, no bile pigments and no sugar in the urine. Liver tests, including glucose tolerance, were negative.

In spite of treatment with diet and high vitamin doses, especially Vitamin B complex, the patient's health deteriorated. She lost weight continuously. Her skin became very dry. Some pigmentation appeared in the face, abdomen, arms and legs. The liver became greatly enlarged, reaching almost down to the Crista pelvis. It was very hard and rough. No enlargement of the spleen could be ascertained.

Laboratory findings (July 1946) — Blood:

Sedimentation Rate (Westergren Technique):

One Hour 12 mm. (Normal 3 to 5 mm.)

Two hours 32 mm. (Normal 7 to 15 mm.)

Sugar Content: 98 milligrams per 100 cc., i.e., 0.098%
(Normal fasting 80 to 100 milligrams per 100 cc.)

Van den Bergh's reaction: Direct, negative. Indirect, negative.

Bilirubin content: 0.24 milligrams per 100 cc., i.e., 0.48 unit
(Normal 0.1 to 0.25 milligrams per 100 cc.)

Cholesterol content: 218 milligrams per 100 cc., i.e., 0.218%
(Normal 150 to 190 milligrams per 100 cc.)

Blood count:

Hemoglobin 71%

Red Blood Corpuscles 4,400,000 per c.m.m.

White Blood Corpuscles 10,000 per c.m.m.

Color Index 0.8

Platelets 264,000 per c.m.m.

Differential count:

Polymorphs 68.0%

Lymphocytes 24.5%

Eosinophiles 0.5%

Hyalines 7.0%

Basophiles —

Red cells:

No apparent changes. Mean diameter — 7.1 (normal).

Punch-biopsy specimens from the liver were examined. Both liver and Kupfer cells were filled with large amounts of hemosiderin. It was surprising that the fibrous tissue was slightly, if at all, increased. However, in some cases of irregular cirrhotic changes, only the softer parts may be aspirated with the needle.

The pathological process taking place was probably as follows: the patient, because of some deficiency of the liver, had been unable to discharge and excrete the great amounts of iron administered to her during her treatment. Hemosiderin was hoarded in the Kupfer and liver cells — a process giving rise to an enormous increase of the size of the liver. It is further remarkable and rather surprising that the spleen apparently did not take an active part in this hoarding process. The liver remained almost exclusively in the pathological foreground. It is further remarkable and rather surprising that there was no excessive growth of the fibrous tissue in the sense of a cirrhosis. No other disturbances in metabolism could be noted. No glycosuria was ever observed and all liver tests remained negative.

It was decided to find out whether the cell cleaning would have an effect on the hemosiderin storage. The daily output of iron in the urine was tested to see whether iron-stores could be mobilized by injection of 50% glucose solution. The following figures were obtained:

Daily iron output measured in 24 hours' urine: 0.309
(average 0.028 mg.)

After injection of 50% glucose on two subsequent days:
1.889 milligrams

Day after: 0.261 milligrams

That is to say, the cell cleaning had the effect that following the injection, the iron output rose six times in the next 24 hours and dropped back to below normal on the day after. This treatment in the way of "liver cell-gym-

nastics," as described later, was carried out for six weeks. The results were that the liver decreased considerably in size, became much softer, and the patient regained five pounds of her weight. The fullness of her liver and the accompanying pain subsided, her appetite increased, and she emphasized that she felt almost relieved from all her troubles.

The fact that all sorts of metabolic products partly of definite hepato-toxic nature can be detained and stored for some time within the liver cells certainly has great practical bearing and may be a help in elucidating some of its features. Products of nutritional individually do not agree with a person, conveyed by the portal blood to the liver and retained in the liver cell, easily may explain allergic phenomena in the liver which are frequently observed when our attention is alerted. An acute edema may develop and cause a considerable enlargement of the liver. Eosinophilia may be present. Vidal's test, which we consider in a way a test for nutritional allergy, becomes positive. The following case illustrates this very well.

CASE REPORT

Mrs. A. S. C. H., 60 years of age, came in complaining of discomfort in the epigastrium and of bloating after eating. This had started two days earlier. She remembered that some time before she had had exactly the same experience, definitely in connection with the in-take of warm bread. Ten days before she had had an attack of flu which made her feel ill and run down.

Upon examination, the liver was found greatly enlarged, the right lobe reaching more than a hand's breadth below the costal arch; consistency was soft. Vidal's test was carried out with 200 cc. milk. The white cells dropped from 7,700 to 6,100, 9% eosinophile cells were present in an otherwise normal disposition of white cells. The urobilinogen in urine was greatly increased and bilirubin was present.

The treatment consisted of intravenous injection of 10 cc. of 50% glucose solution and 10 cc. of 10% saline solution. Within 24 hours the size of the liver had considerably diminished. After 48 hours, all clinical signs had disappeared and no enlargement of the liver could be felt. The patient felt hungry and well. The urobilinogen in urine was scarcely noticeable and the eosinophile cells had dropped from 9% to 5%.

The phenomenon, as exemplified in this case, has been called "urticaria of the liver"* (Pribram). "Cell cleaning" in cases of acute liver intoxication should be carried out as an emergency measure, almost equal to a stomach lavage after poisoning. Serious damage to the liver may often be effectively prevented by this simple measure of precaution.

The question has been raised about the incidence of thrombosis following injections of highly hypertonic solutions. The answer is that this danger is practically non-existent, provided the injection is performed with correct technique. Blood has to be reaspirated into the syringe and paravenous leakage avoided. Overcautious persons may add some heparin.

THE PRINCIPLES OF LIVER-CELL GYMNASTICS

Since the experimental work of A. Forsgren, we know that the liver cell works in a special rhythm and

* Pribram, B. O. C.: International Congress, Vichy, 1937.

that the different metabolic functions are separated not only in time but apparently take place in different zones of the liver cell. There are even different functions within one liver lobule (Geraudel-Elton). Every liver unit, probably every liver cell, has a certain store of different metabolic products, that is to say, there are not only carbohydrate stores in the form of glycogen but also stores of bile pigments (although normally not in a microscopically visible form) and probably protein stores. Foreign substances given orally or intravenously are removed from the blood and stored within the liver cell until gradually released and excreted in a special rhythm.

Forsgren and his co-workers found that between the two phases of assimilation and dissimulation or secretion, the actual size and weight of the liver undergoes considerable changes. At the height of the dissimulatory phases, Forsgren found the rabbit liver to drop from 140 gm. to 50 gm. The cells become small and the glycogen content may drop from 13% to 1%. Forsgren insists upon the fact that an *intrinsic* functional rhythm exists independently of intake of food. The changes of day and night determine the rhythm of the activity of the liver cells. The secretion starts at the periphery of the lobules and spreads to the center, while assimilation begins at the center. During the assimilatory phases not only are glycogen and protein stored, but water as well. Bearing in mind this rhythmic function, we can easily understand why a simple flooding of the liver cells with glucose is not an adequate method of improving the liver cell function. Glycogen supply certainly fulfills the task of aiding the liver cells in their assimilatory phases. On the other hand, when the liver cell does not store glycogen, it is rarely due to the fact that no glucose is available for this purpose. In most cases it is because the damaged liver cell has lost its function of storage. However, when there is no actual lack of glycogen and the liver cell is able to store, the glycogen stores are filled from the very first days and no more can be obtained by further flooding with glucose. Normally, carbohydrate intake by mouth is quite sufficient. Should we wish to influence the activity of the liver cells, we must try to strengthen these activities by other therapeutical methods. We cannot build up and strengthen a muscle by keeping it permanently in a state of tension, but by inducing a rhythmical change between tension and relaxation. This idea has led to the introduction of what I have called the liver cell gymnastics.

While with an ample supply of glucose we are in a position to favor and to reinforce the assimilatory function, we are able, on the other hand, through the application of thyroxin, to stimulate the dissimulatory phases, thus increasing the amplitude between assimilatory peak and dissimulatory trough; in other words, increasing the *work volume* of the cell. If applied in a practical way, one could conceive that this training might lead to increased functional activity of a damaged liver cell.

Following the above-explained conception, the correct thing to do would be to supply glucose in conformity with the *intrinsic rhythm* of the liver cells.

Obviously this is not practicable. Moreover, our experience has proved this to be unnecessary so that we are able, through training, to *force upon the liver cell an extrinsic rhythm according to our choice* in the course of our treatment. The curves obtained may serve as an illustration of this biologically significant effect. The scheme of treatment is as follows: after a general "cell cleaning" through intravenous injection of 50% glucose solutions on two days, the actual liver cell gymnastic starts: two days of high glucose supply, including eight to ten units of insulin per day, with the aim of stimulating the assimilatory phase of the liver cells, are followed by two days of freedom from all carbohydrates with the injection of thyroxin (1 mg.) — a substance which stimulates the dissimulatory phases and a depletion of the glycogen stores.

The influence of insulin on the storage of glycogen has been doubted in recent times. While many physicians are clinically convinced of the favorable influence of insulin on storage function, experimental medicine has begun seriously to doubt this effective role (Forsgren, Straub, Brentano, Althausen). The latter, without challenging the clinical value, maintains that the effect of insulin-glucose administration is probably different from that assumed up to now.

Based on experiments on animals it is maintained that any lowering of the blood sugar level, as caused by insulin, initiates the depletion of glycogen stores in the liver (Soskin). The addition of insulin to glucose might, therefore, counteract the desired glucose storing effect. However, recent "tracer-experiments" (N. O. Kaplan and D. M. Greenberg) with radioactive phosphates have again confirmed that insulin produces or favors a general storage in the liver and muscles. Our own clinical experience has afforded manifold evidence of the value of insulin.

J. A. Schindler reported dramatic and convincing results with the addition of insulin to glucose in a case of portal cirrhosis. They could not be obtained with glucose alone. Crandall demonstrated again that when hyperglycemia exists, insulin facilitates the deposit of glycogen in the liver.

Whatever the meaning of the divergent results of experimental physiology might be, the author cannot agree with the opinion that the administration of eight to ten units of insulin in addition to glucose is valueless or damaging. He has seen numerous cases where the benefit of insulin was not questionable and indeed impressive. Oral application of larger amounts of glucose was much better tolerated when some insulin was given in addition. Anorexia, nausea, and vomiting stopped dramatically in some instances while glucose alone did not change these conditions. Similar observations were made by many observers. The divergence between clinical experience and experimental medicine can be explained.

Pathological conditions in patients suffering from acute hepatitis are extremely complicated. In many cases, the clue for explaining the apparently contradictory observations lies, to the writer's opinion, in the fact that the pancreas frequently is affected simultaneously with the liver. Tolerance for insulin is considerably increased in many instances up to 120 to

210 units (Pavel et al.). The author, based on his clinical experience, warmly recommends a revival of the insulin addition in the glucose treatment of hepatitis.

THE PRINCIPLES OF LIVER-CELL GYMNASTICS

During the past twelve years we have systematically tried out the liver cell gymnastics on a number of patients with impaired hepatic function, especially in patients with hepatitis and cirrhosis.

Forsgren maintains that the intrinsic rhythm of the liver cells is so strong that it can hardly be influenced either by food intake or by the state of sleep and wakefulness. The course of the curves he obtained was independent of meal hours. Apparently sleep exerts no regular influence either because a trough taking place in the early evening may have begun in the afternoon, several hours before the animal sleeps, and may be followed by a rise in the latter half of the night during sleep. In contrast with his skeptical observations, we believe that the influence of our rhythmic treatment on the liver cell activity has been established beyond any doubt.

By means of continuous curves we have determined the bilirubin and blood sugar content of the blood serum, obtaining clear rhythmic curves which may be considered as more or less the expression of liver cell gymnastics.

The functional liver cell gymnastics are by no means confined to carbohydrate metabolism. They influence in an analogous way the bilirubin, cholesterol and urea metabolism. The glucose-insulin days represent the assimilatory days of storage in general, whereas on the thyroxin days the cell is squeezed out, so to speak, and the products of metabolism are absorbed into the blood stream. The troughs correspond

to the insulin days; the peaks to the depletion of glycogen, i.e., to the squeezing out of the cell on the thyroxin days.

On the G-i* days we observe a drop in the blood sugar and of the bilirubin values. On the thyroxin days, there is a rise of the blood sugar and of the bilirubin values. For example, in icterus the bilirubin values

* G-i — glucose-insulin.

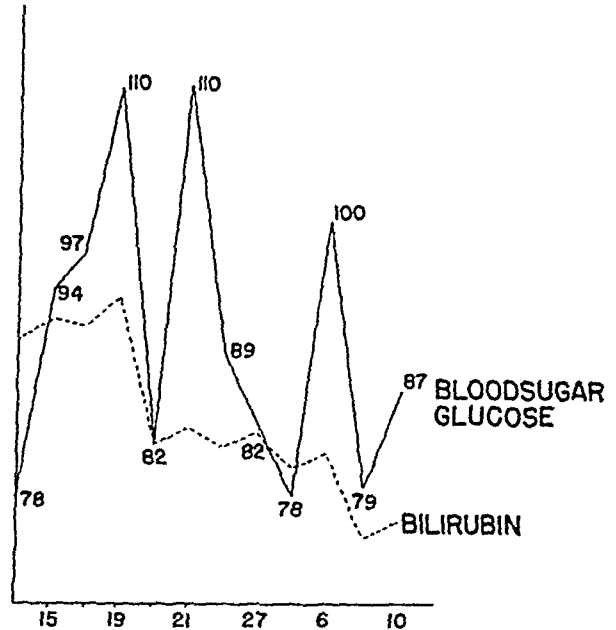


Figure 1 — Patient suffering with catarrhal jaundice. Rhythmical curve of blood sugar and bilirubin showing the influence of alternating G-i and Thyroxin days. The peaks of the curve correspond to the thyroxin days and the troughs to the G-i days.

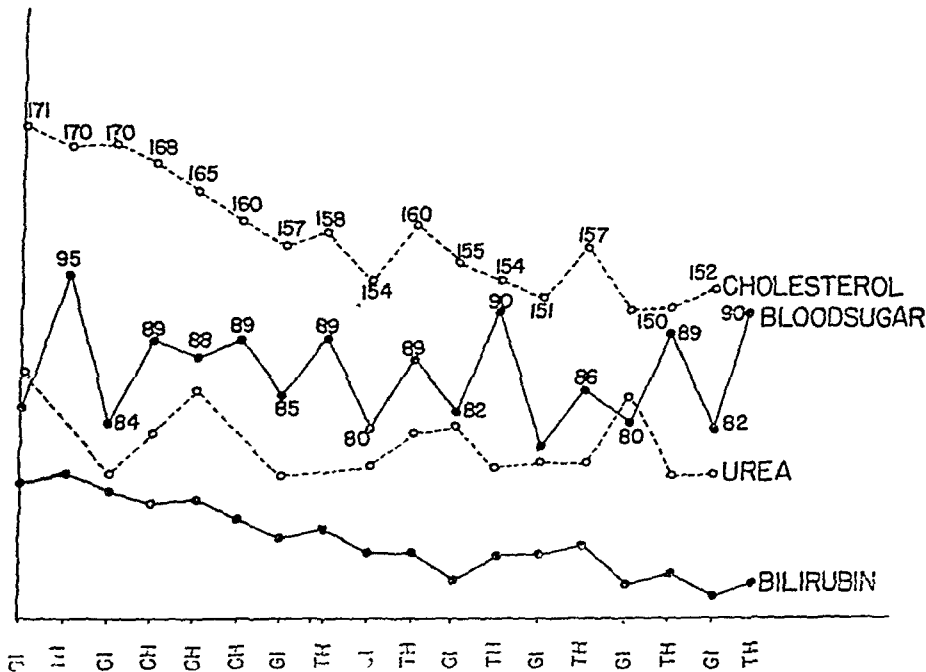


Figure 2 — Rhythmical curves of cholesterol, blood sugar, urea and bilirubin in a patient suffering with sub-acute hepatitis.

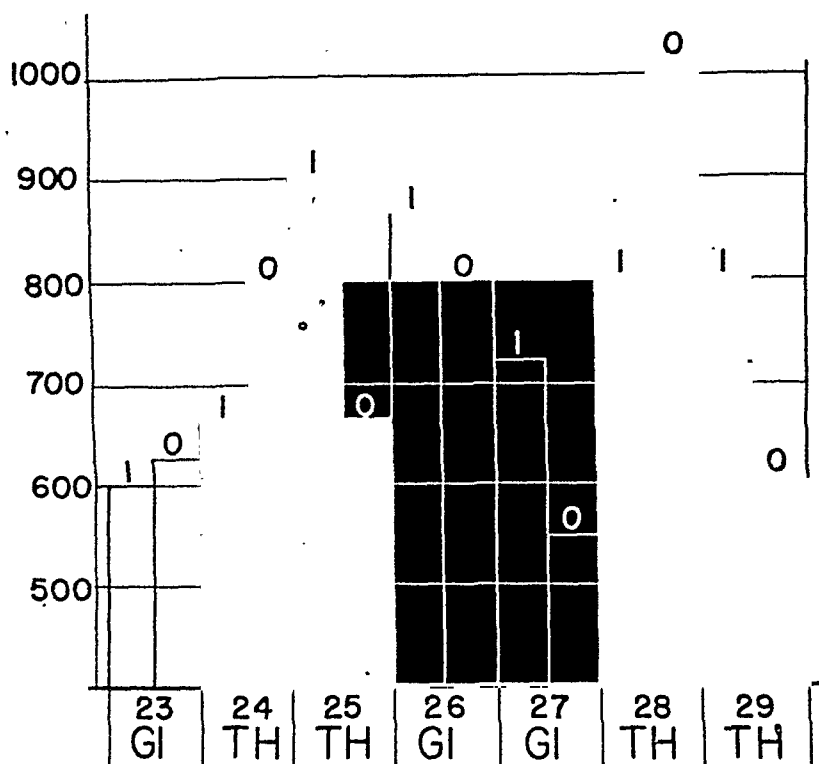


Figure 3 — This curve shows the influence of the Liver Cell Gymnastics on intake and output of water. Note the increase of output on the days following the change of treatment.

descend step-like until they reach the normal stage, while when we resorted to the simple insulin-glucose therapy, an initial sudden descent was followed by a very gradual, long-retarded decline.

TECHNIQUE

We started as already mentioned by injecting a hypertonic glucose solution (20 cc. of a 50% glucose solution) intravenously. Then the liver cell gymnastics were started in the following manner: two days of glucose-insulin treatment were followed by two days of thyroxin injections with complete omission of carbohydrate from the diet. These rhythmic gymnastics were continued for six weeks (see curve).

On the glucose-insulin days, the patient had full diet, rich in proteins with restrictions in fat. Only genuine fresh butter or olive oil was allowed. We did not limit our investigations to the carbohydrates, but estimated all the main products of cellular metabolism in the blood. The result was that not only glucose, but bilirubin, cholesterol and proteinogenic substances, such as urea, followed a similar rhythm. All these products diminish in the blood on the days of cellular assimilation and increase under the influence of thyroxin and hunger. The curve in Figure 2 serves as an illustration of the rhythmic oscillations under the influence of cell gymnastics in a patient suffering from acute icteric hepatitis (catarrhalic jaundice). This patient underwent the normal glucose-insulin treatment without any change in the bilirubin level for five weeks.

We have tried this method of treatment on a total of twenty patients suffering from sub-acute chronic

hepatic insufficiency, in many types of hepatitis and especially in cases of cirrhosis. In the latter cases particularly, the results could be called convincing and sometimes even dramatic, all the more so as the results obtained by the usual methods of treatment have been very poor indeed.

It seemed of interest to extend our research to the exchange of liquids; that is to say, to general water metabolism in the liver. The intake and output of liquids has been measured and illustrated by curves. The curve in Figure 3 proves the interesting fact that diuresis increased and exceeded liquid intake, especially on the days when a change was made from one phase of cell gymnastics to the other, whatever these phases may have been respectively. The shaded columns indicate the insulin days and the first columns show that the diuresis somewhat exceeds the fluid intake. Next, we change to thyroxin and from the very first day, the output is seen considerably to surpass the intake. When in the next phase we changed from thyroxin to insulin, the output again surpassed the intake in a remarkable manner. The same thing occurs whenever a change occurs from the insulin to the thyroxin phase.

The following case furnished a good example of the dehydrating effect of the liver cell gymnastics and of the often considerable increase of diuresis, leading to the greater output of liquid. The accompanying curve shows the way in which routine therapy led to a dead-end whereas the initiation of liver gymnastics immediately brought about dehydration and increased diuresis.

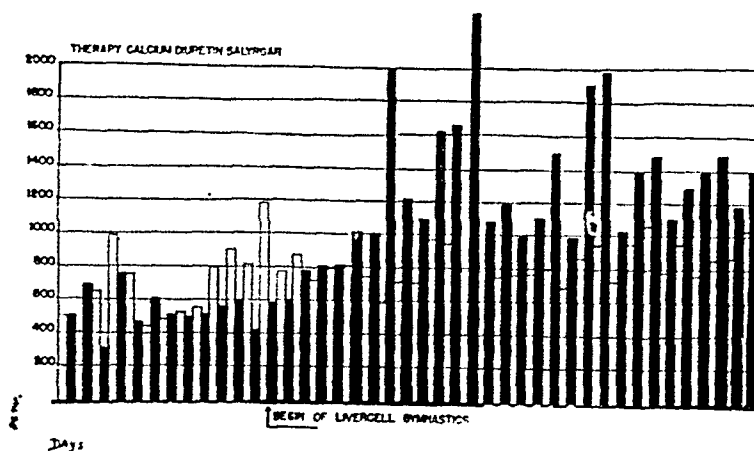


Figure 4 — This curve shows the effect of the Liver Cell Gymnastics on the patient suffering from cirrhosis where dehydrating treatment, combined with calcium, diuretin, and salyrgan has led to a dead end. Note the increase of output as marked in the dark columns surpassing by far the intake of liquids marked in white columns.

CASE REPORT

Patient, Dr. St. Anamneses: Father alcohol addict. Patient himself is a moderate drinker, consuming weekly one-half to one bottle of Moselle, occasionally beer, very seldom brandy. For some time past, he has had digestive trouble, a sensation of flatulence, and a feeling of pressure. After a banquet, he had severe diarrhea, accompanied by melena.

Findings: A thick-set man of medium stature. Abdominal walls rich in fat; the liver extended four fingers' breadth below the costal arch; margin of liver hard. Examination of the digestive tract showed no cause for the hemorrhage. Accordingly it is assumed to be a hemorrhage due to portal hypertension in cirrhosis.

Urobilinogen markedly positive.

Treatment by liver cell gymnastics from January 21 to March 3, 1935. Excellent results. Patient was completely relieved of his complaints. At dismissal, the liver hardly projected beyond the edge of the ribs. The accompanying curve relating to intake and output of water during the gymnastics is very instructive. The first part of the curve shows the effect of insulin and of injections of a high percentage of glucose solution only. During the first few days the output of liquid exceeded the intake, a sign of dehydration. But this effect soon subsided. At this stage the liver cell gymnastics were started. An

enormous increase of fluid output could be noted, continuing until near the day of dismissal. The patient, a busy physician, reported on his condition in several letters. He was feeling completely free from pain and discomfort and was able to resume his practice.

DISCUSSION

We have expressed the opinion that the characteristic zig-zag form of the metabolic blood curve pictures liver cell activity; in other words, a reduction of the elements of metabolism contained in the blood corresponds to the assimilatory phase of cell storage which occurs on the G-i days while the increase of the metabolic products in the blood corresponds to the dissimilatory phase, i.e., to the squeezing out of the cell.

It might be objected that a drop in the curve on the G-i days could be caused only by the fact that on those days choleresis and diuresis increased and that, therefore, more products of metabolism are excreted, while on the thyroxin days both choleresis and the diuresis are reduced.

In order to clarify this point, we conducted the fol-

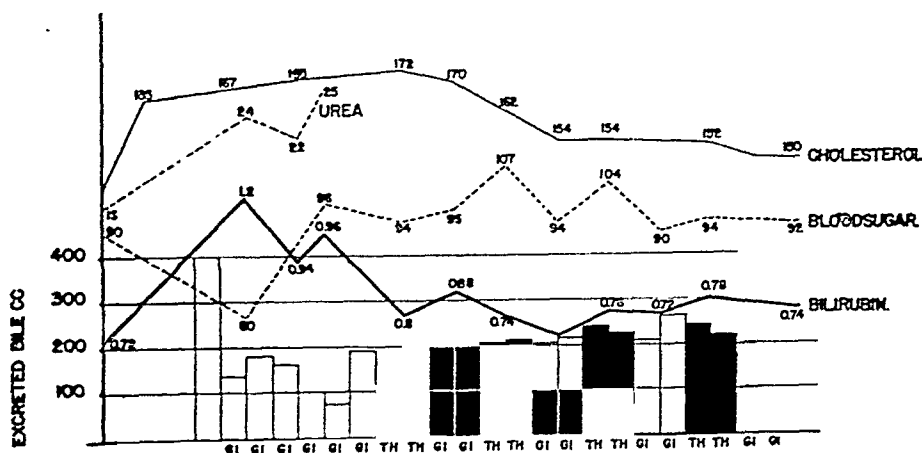


Figure 5 — This curve shows the comparison of the blood curves with the excretion of bile. Note that the increase of bile output corresponds with the peaks in the blood curves.

lowing experiment on a patient who had to undergo cholecystectomy.

After cholecystectomy, drainage of the common duct was carried out by introducing a rubber tube downwards to the papilla. The wall of the common duct was stitched water-tight around the tube to avoid leakage. During the liver cell gymnastics (started a few days after the operation), an exact measurement was made of the intake and output of liquid, and in addition, of the quantities of bile eliminated through the tube. The elimination of bile through the tube proceeded very regularly, about four to five drops a minute, and the average daily elimination varied between 300 and 370 cc. This experiment supplied a clear answer to our question, as illustrated in the curve in Figure 5.

The uppermost curve is the cholesterol curve, the second one the glucose curve, and the lowest, the bilirubin curve. The shaded columns indicated the amount of bile eliminated on the G-i days, the dark columns show the bile elimination on the thyroxin days. It plainly can be seen that with the peaks of the curves indicating the increase of these products in the serum on the thyroxin days, there is a *simultaneous* increase of bile drainage. This proves that on these days the liver is virtually "squeezed out" and that the increase of products of metabolism in the blood is not caused by a retention and diminished choleresis and diuresis.

FOLLOW-UP RESULTS

It was interesting to note that the improvement had continued when the patients were re-examined over a period from one to two years. The outbreak of the war brought the follow-up work to an end. I there-

fore refrain from making any statement as to how long improvement lasts and whether the liver cell gymnastics can indeed bring the process of liver destruction to a certain standstill through stimulating of function and perhaps of regeneration. But, I do believe that this scheme of treatment is worth trying as it involves no risks whatever. The scheme for liver cell gymnastics described above is, of course, only one way of influencing the rhythmical activity of the liver cells. We have tried other ways, and many more may yet be found. We have substituted thyroxin by extracts of adrenal cortex. We have exercised another rhythm by a scheme of two days of full diet alternating with two days of complete fasting, continued for six weeks! Injections of hypertonic solutions were followed by injections of distilled water. The influence of all these rhythmic schemes on the metabolism is remarkable indeed, and I believe the conception merits further clinical investigation.

SUMMARY

It is demonstrable that the intravenous injection of the 50% glucose solution has a "cell cleaning" effect by helping the liver cell to discharge all sorts of hoarded products including fat, iron pigment, and bile pigment, etc. The metabolic functions of the liver cell take place in an intrinsic rhythm separated in time and space for the different products.

By alternating stimulation of the assimilatory and dissimilatory functions, we are able to force upon the liver cell an extrinsic rhythm in enlarging the rhythmic work-volume of the liver cell in a sort of "cell gymnastic" to improve the functional vitality of liver cells and to obtain therapeutical results in cases of chronic hepatitis.

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Ileo-Colic Fistula due to Cancer of the Descending Colon. Operative Results

By

ALEXANDER STRELINGER,
M.D., M.Sc., F.A.C.S.
ELIZABETH, N. J.

PRESENT KNOWLEDGE indicates that surgery and radiation are not the ultimate answer to malignant disease. However, their usefulness at present is paramount. Due to better bio-chemical knowledge of the body, to the use of blood, blood substitutes, minerals, amino-acids, oxygen and suprarenal cortex and to improved anesthesia technics, surgical procedures of considerably large extent became possible. These in turn permit to advance the limits of operability. Dr.

Alexander Brunschwig published a volume describing 100 cases of malignant disease, all of which would have been considered inoperable ten or fifteen years ago, now all treated surgically, and obtaining considerable palliation, in few cases cure.

This is a report about a patient who had a cancer of the descending colon, perforating into the ileum, with extension into the mesocolic glands and to the abdominal wall, and who obtained palliation by extensive surgery.



Figure 1 — Barium enema showing the ileo-colic fistula due to a carcinoma of the descending colon.

CASE REPORT

This patient was referred by Dr. Gerard and was first seen by me on Dec. 22, 1946. She was a 43 year old woman, married. Her complaint was, that for eight months she had severe abdominal cramps in the upper abdomen, and she lost considerable weight. History otherwise was non-contributory. Physical examination disclosed an anemic and toxic looking patient, who had obviously lost much weight. There was a tumor of hard consistency, about the size of a small grapefruit, on the level of the umbilicus in the left half of the abdomen, and it was not movable. Otherwise physical examination was irrelevant. The x-ray films of a barium enema taken by Dr. Gerard, disclosed that a 10 cm. length of the descending colon has irregular, fuzzy edges, with considerable narrowing of the lumen on the highest 3 cm. length of the abnormal appearing bowel. The cephalad loop of normal bowel lost its normal contours abruptly at its junction with the abnormal loop, the lumen narrowed acutely; at the junction of the abnormal loop with the normal caudad loop the transition to normal was more gradual. At the middle of the abnormal loop there was an irregular 1 to 2 mm. wide, 2 cm. long radio-opaque strip visible jutting out from the medial edge of this loop towards the midline of the body. Laboratory data: Urine: non-essential. Blood count. RBC, 2,900,000. Hemoglobin, 10.5 grams. WBC, 7,600. Differential, not essential. Prothrombin time, 80% of normal. Total serum protein, 7.3 gr. Albumin, 4.9 gr., globulin, 2.5 gr.

The patient was admitted to the St. Elizabeth Hospital in Elizabeth, N. J. On Dec. 30, 1946, a laparotomy was done by incision in the right upper quadrant. The abdomen was explored manually. The tumor was found to be an integral part of the descending colon; it was adherent to the inner surface of the anterior abdominal wall; several infiltrated glands were felt in the mesocolon. There were no palpable metastases in the pelvis, in the liver, or in the spleen. A Devine-type colostomy was done in the right upper quadrant. Uneventful recovery followed. The patient was soon discharged with a functioning colostomy to be re-admitted later for possible resection. The patient experienced relief of the abdominal cramps; but her general appearance did not improve. She also mentioned that small amounts of fecal matter were passed by rectum. This continued up to her readmittance to the same hospital.

On Jan. 31, 1947, she was re-explored by a left para-



Figure 2 — After evacuation.

median incision. The manual findings of the first operation were confirmed but in addition to them, it was found that a loop of ileum is firmly attached to the tumor. The local extensions, and the infiltrated mesocolic glands, indicated that permanent cure can hardly be hoped for, no matter what kind of procedure is done, if any at all. But it seemed logical to attempt a block resection of all the structures visibly and palpably involved by malignant disease. This was carried out in the following manner. Beginning at the left paramedian incision, the peritoneum and the transverse abdominal muscle were transversely incised above and below the attachment of the tumor to the anterior abdominal wall. A flap consisting of the peritoneum and the transverse abdominal muscle was peeled off, limited by the mentioned incisions and the laparotomy wound, and cut away from the abdominal wall lateral from the tumor attachment. The tumor was thus freed from the abdominal wall. Then the transverse colon was bisected between clamps just proximal to the ileal flexure, and the sigmoid likewise at its middle. From the points of section, the colon between these points, and the corresponding mesocolon, were now mobilized and freed by resection of the mesocolon and ligation of the left colic vessels. The structures involved by tumor were now only attached to an ileal loop. Well above and below the attachment the ileum was bisected between clamps. Resecting the corresponding mesoileum completed the block resection of all tumor-bearing area. The operation was completed by an end-to-end ileo-ileostomy, and by blind closure of the transverse colon and of the sigmoid. This latter was necessary, because the gap was too extensive for anastomosis. The abdominal wall was closed by overlapping the distal layer of muscles over the proximal layer. The resected specimen consisted of the structures mentioned. The tumor was a fungating carcinoma. It was broken down to large extent and it caused perforation of the colon into the ileum. The irregular narrow stricture projecting medialwards found on the radiograms obviously corresponded to this communication between the lumina. The fistula accounted for the continued passage of small amounts of fecal material in presence of the colostomy. The microscopical diagnosis was: adenocarcinoma grade II; infiltrating and perforating adjacent ileum; having the morphology of carcinoma.

For a few days after this operation the patient was critically ill; with the use of the supportive measures mentioned in the introduction she rallied. She left the hospital two weeks postoperatively. She gained considerable weight, her strength improved, the toxic ap-

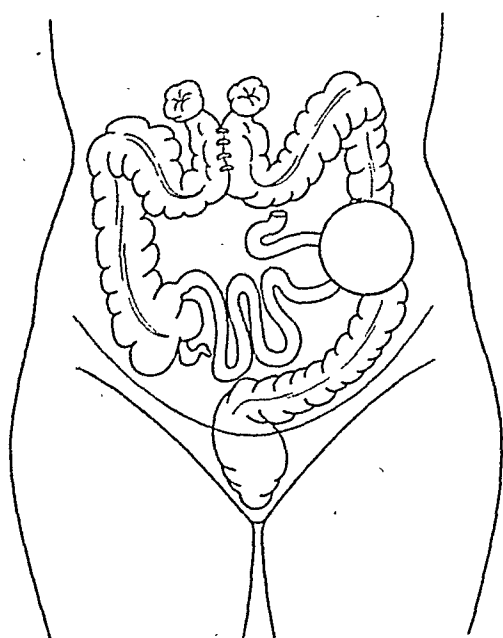


Figure 3 — Findings on physical examination.

pearance abated, and her blood count returned to normal. Though it was particularly stressed to the husband of the patient, that ultimate prognosis is bad, he was impressed by the improvement in the patient's appearance. He repeatedly requested that the patient shall be subjected to an operation for the purpose of re-establishing her intestinal continuity, i.e., passage towards and through the rectum and closure of the colostomy. The patient, not knowing that she had cancer, insisted on it too. It was planned to use the procedure published by Harvey Stone: to isolate a suitable length of ileum, leaving its blood supply undisturbed; to splice this into the blind ends of the transverse and of the sigmoid colon by anastomoses and to connect the loose ileal ends by anastomosis. On April 21, 1947, a laparotomy was done. Extensive retroperitoneal metastases were found, and the planned procedure abandoned.

The patient left the hospital on the eleventh post-operative day with a well functioning colostomy. Even though she already has extensive recurrence, her general

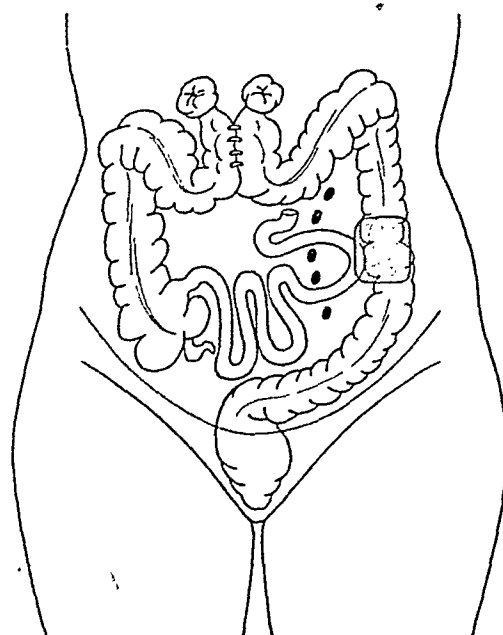


Figure 4 — Findings at exploration. The shaded area indicates the adherence of the tumor to the parietal peritoneum.

condition is much better both subjectively and objectively than before the resection. The improvement is impressive. In view of such degree of palliation the operative procedures seem to be adequately justified.

SUMMARY

A case of a fistula of the ileum and of the descending colon is reported. The presence of perforation of the colon was suggested by the radiological findings, though the diagnosis of ileo-colic fistula was not made by these means. This diagnosis was made and its cause identified only at operation. It was a cancer of the descending colon extending into the ileum and into the abdominal wall, and causing metastases into the mesocolic glands. An extensive block-resection encompassing all structures involved by the process was carried out with marked temporary improvement of the patient.

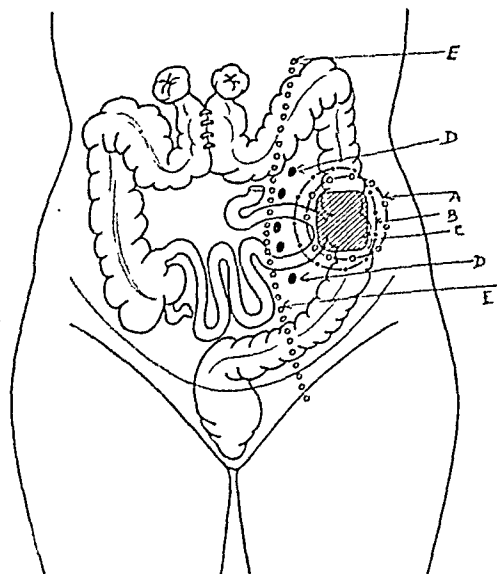


Figure 5 — Detail findings at the resection. A: Limits of the resection of the inner layer of the abdominal wall. B: Size of primary tumor. C: The shaded area indicates the adherence to the abdominal wall. D: Infiltrated mesocolic glands. E: Extent of resection.

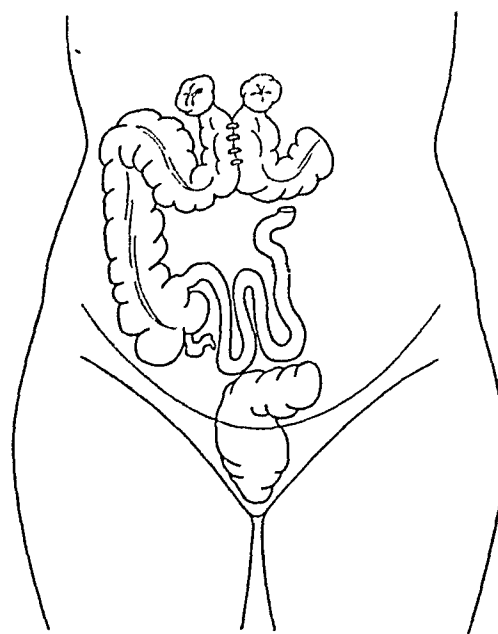


Figure 6 — Status following the resection.

Editorial

ULCERATIVE COLITIS

THE RECENT EDITORIAL by Beaumont S. Cornell on the psychogenic factor in ulcerative colitis is exceedingly interesting. I have had long clinical experience with this disease; my first article appeared in the *Annals of Internal Medicine* in 1927. I quoted Pargen's and Logan's paper on the Etiology of Chronic Ulcerative Colitis, published in 1923. They found a Gram positive, lancet shaped diplococcus which formed colonies in the submucosa, causing the frequent recurrences of the disease. The culture of the diplococcus is difficult; it grows readily in brain broth culture, but its isolation from other bacteria requires bacteriologic skill and patience.

The early acute cases are limited to the rectum and pelvic colon. L. A. Buie of the Mayo Clinic gave the first accurate description of the edematous hemorrhagic membrane, followed by various gradations of ulcers, as visualized by the sigmoidoscope. This early form occurs more frequently in young adult females who have undergone some sudden psychological stress. The treatment consists in the mineral oil nightly retention enema and the Barger vaccine. The mineral oil quickly reaches the cecum, is not a culture medium, discourages the growth of all bacteria, and is easily retained. The "Cure" results in from three to six weeks' time; the diet is bland and of high vitamin content. The acute fulminating form involving the entire colon is attended with very high mortality, us-

ually terminating in perforation and acute peritonitis. This type occurs very rarely.

The diagnosis of the chronic type is made by the barium enema, the haustration disappears, the colon is shortened, and the feces contain much mucus, blood, and large variety of bacteria. The pathologists have described "a colonic wall very thick, with loss of elasticity and the mucosa practically absent replaced by a fibrohemorrhagic exudate" (Dr. George Ives). Treatment consists in the employment of the Barger vaccine, mineral oil retention enema and high vitamin smooth diet, after the colon begins to show improvement in caliber and length air insufflations are given. In my book on *Clinical Gastro-Enterology* I display x-ray films of complete restoration to normal following this form of treatment.

The severe chronic type requires surgical intervention. *Ileostomy* is the operation of choice, and if the diseased colon continues to produce toxic symptoms, complete colectomy is performed. I have records of patients who maintain a good state of nutrition for many years following the operation.

I agree with Dr. Cornell's final statement, "In a person of sensitive temperament harboring a dormant intestinal infection, a sudden psychological stress might be expected to favor a precipitation of active inflammation."

H. W. SOPER, M.D.
St. Louis, Mo.

Obituary

ON JUNE 26, 1947, Dr. John Leonard Kantor died suddenly at the age of 57 at Mt. Sinai Hospital, New York. With his passing, the medical profession loses a great scientist and teacher; his family loses a devoted and sincere father and we all lose a friend who was always genial, thoughtful, happy and good-natured.

John L. Kantor was born on April 12, 1890, the son of Dr. William L. Kantor and Mrs. Katherine Gordon Kantor. He received his A.B. degree at Columbia University in 1908, and his Ph.D. and M.D. degrees at Columbia in 1912.

He was a diplomate of the American Board of Internal Medicine and a fellow of the American College of Physicians, the New York Academy of Medicine and the American and New York Gastroenterological Association, of which he was a former president.

Other organizations in which he held membership included the American Roentgen Ray Society, the American Medical Association, the Association of Military Surgeons, the Medical Societies of the State and County of New York and Phi Beta Kappa, Sigma Xi, Alpha Omega Alpha and Phi Delta Epsilon.

A veteran of both world wars, he retired with the rank of Colonel on August 16, 1945. He entered as First Lieutenant and Assistant Chief of Medical Service, in the U. S. Army General Hospital No. 14, in Fort Oglethorpe, Georgia. In 1918, he organized and directed the Section of Gastroenterology. In 1935 he was Commanding Officer of General Hospital No. 82. He was Chief of the Medical Service of the First Evacuation Hospital at Plattsburg Barracks in 1939. In 1940 he was Chief of Medical Service, First Evacuation Hospital at Madison Barracks. In 1940 also, he helped prepare new T/O for General Hospital for the Surgeon General, suggesting that a section of Gastroenterology be included therein and that the dietitians be also included. He was ordered to active duty on July 15, 1942. From July 15, 1942 to December 28, 1942, he was Commanding Officer of the 36th (redesignated 136th) General Hospital; he was Executive Officer of the Hospital Training Area, Camp Carson, Colorado from July 28, 1942 to October 29, 1942; he was Commanding Officer of the 49th General Hospital at Camp Carson, Colorado, from December 28, 1942, to February 10, 1943; from February 12, 1943 to January 8, 1944, he was at Chickasha, Okla-

homa; from February 28, 1944 to December 15, 1944 he was at Base A, Milne Bay, New Guinea. He retired on August 16, 1945.

In 1919 Dr. Kantor became Chief of the clinic for gastro-intestinal diseases at Vanderbilt Clinic, Columbia University. He remained in that position until 1935. He also held concurrently many other posts, including those of gastroenterologist and associate roentgenologist at Montefiore Hospital, gastroenterologist at Beth David Hospital and consultant in the same capacity at the Will Rogers Hospital in Saranac Lake, New York, the National Jewish Hospital in Denver and Sharon (Connecticut) Hospital.

Dr. Kantor was an associate in medicine at Columbia beginning in 1924. Since 1939 he had been associate clinical professor of medicine there. In teaching gastroenterology in post-graduate courses at Montefiore Hospital he got the inspiration for his extensive literary work.

He published two books, namely "Treatment of Common Disorders of Digestion," C. V. Mosby Co. (first edition, 1924; second edition, 1929), and "Synopsis of Digestive Diseases," C. V. Mosby Co. (1937), (Spanish edition, 1941). He also contributed to Appleton's "Practitioner's Library of Medicine and Surgery," and to Portis's "Diseases of the Digestive System." In addition, he wrote many articles on gastroenterology, gastrointestinal roentgenology and military medicine. Among his chief contributions were papers on Anomalies of the digestive tract, especially the colon; functional disorders of the colon (in which he introduced the term "unstable colon" in 1931); roentgen diagnosis of ileitis (introduced the term "string sign" in 1934); roentgen diagnosis of steatorrhea (described "moulage sign" in 1939); role of digestive disease and the utilization of gastroenterologists in the U. S. Army.

He was Associate Editor (Military Gastroenterology) "Gastroenterology" (official journal of the American Gastroenterological Association).

In 1931, he gave an oration at the Southern Medical Association in New Orleans on "The Unstable Colon." He was essayist at the Fourth International Congress of Radiology at Zurich, Switzerland in 1934. He was Guest Speaker at the Postgraduate Medical Assembly of East Texas in Houston, Texas, in 1934. He helped organize the Section on Gastroenterology and Proctology for the Medical Society of the State of New York in 1937. On November 3, 1942, he delivered the Friedman Lectures at the National Jewish Hospital at Denver.



DR. JOHN L. KANTOR

In his passing the world loses a great teacher of gastro-enterology. His many associates, students and friends lose a great and inspiring leader, to whom they owe much for his suggestions, encouragement and helpful criticism. In his long and successful career in medicine he was in a measure largely responsible for the modern conception of medical education. His lectures and conversations were often interspersed with morsels of humor which he used to illuminate his point. This capacity for humor made him an invaluable after-dinner speaker.

Although Dr. Kantor has passed on, the writer, who has been closely associated with him for over twenty-two years in his clinical and teaching capacities, knows that his contributions to gastroenterology will live on.

BERTHOLD WEINGARTEN, M.D.

Book Reviews

Colloid Science: A Symposium. Pp. 208 (\$6.00), Chemical Publishing Co., Inc., Brooklyn, N. Y., 1947.

The text of this symposium was taken from a series of lectures given as a course in colloid science at Cambridge University, Cambridge, England, under the auspices of the Royal Institute of Chemistry. Its publication is justified by the growing interest in colloid

systems, polymers and macro-molecules. The study of "interfacial phases" serves as a background for attack on the more complex case of the disperse systems and for interpreting the phenomena encountered with matter in the form of films, membranes and fibers. No doubt the biological topicalness of macro-molecules and enzyme systems will prompt many physicians to read this admittedly technical treatise.

Physiology of Man in the Desert. By E. F. Adolph, Pp. 357 (\$6.50), Interscience Publishers, Inc., New York, 1947.

This most interesting volume is the work of the Rochester Desert-Unit who made a careful physiological investigation of "man in the desert" during World War II. The names of the associates of Adolph represent physiologists, botanists and pharmacologists. The book goes into detail with respect to the various studies made by this group and the general results expressed very succinctly by Adolph on page 20 are as follows: "In general, the requirements of man in the desert are simple enough. The only means of keeping the body cool is to sweat; the only means of keeping up the water content of the body is to drink as rapidly as one sweats. The only means of avoiding both is to stay out of the desert." Thirst cannot really be relieved by anything except water. The work approaches the subject from the standpoint only of man's relations to heat and water. The book should be of basic importance from a military standpoint. It also clarifies many questions that an internist naturally has revolved in his mind.

English-Spanish Chemical and Medical Dictionary. By Morris Goldberg, Pp. 692 (\$10.00), McGraw-Hill Book Co., Inc., New York, 1947.

This dictionary should prove invaluable at the present time, because of the increasing influence of American

medicine in Latin America, because of the definite increase of interest by American scientists and physicians in South American medical literature and particularly since this fairly complete dictionary is such a marked improvement on the few existing bilingual dictionaries previously available. No doubt Goldberg's contribution will fill a definite need.

Infant Nutrition. By P. C. Jeans, A.B., M.D. and W. M. Marriott, B.S., M.D., Pp. 516, C. V. Mosby Co., St. Louis, 1947.

This text-book approaches the title subject from a wide-angled viewpoint, devoting sufficient space to feeding formulae, but not neglecting those diseases of infants which so directly affect the nutritional status. There is an interesting section on "well-water cyanosis." Both human and bovine milk are exhaustively described. The chapter on the celiac syndrome has the advantage of simplicity and clarity. Prematurity, the avitaminoses and miscellaneous techniques covering laboratory examinations and transfusions in infancy round out a text which is attractive for its practical usefulness and comparative brevity.

BOOKS RECEIVED:

Disfunciones Motoras Del Estomago. By E. Arias Valles, Madrid, Spain. 1947.

Abstracts Of Current Literature

CLINICAL MEDICINE

Stomach

MENZES, H.: *Secondary lymphosarcoma of the stomach.* (Rev. Basil de Med., Vol. 14, No. 3, March 1947, pp. 177-179).

A case is described of primary lymphosarcoma of the cervical region with secondary localization in the stomach. There was no other evidence of metastases, although the skull was omitted from examination.

CASH, I. I. AND RAPPOPORT, A. E.: *Reticulum cell sarcoma of the stomach.* (Gastroenterology 6, 1, 40, January 1946).

A rare case of reticulum cell sarcoma of the stomach is reported. These cells are derived from the germinal centers of the lymphoid tissue located in the gastric sub-mucosa. Clinically the symptoms are protean as in gastric carcinoma. Gastroscopically, the lesion appears not unlike that of an infiltrating lymphosarcoma. The lesion tends to ulcerate and infiltrate surrounding organs, and in this case, a "forme fruste" perforation was present.

The roentgenological examination revealed an extensive prepyloric lesion which appeared polypoid in nature with small and large filling defects in the distal third of the stomach and marked enlargement

and distortion of the gastric rugal pattern over the small area proximal to this. Some peristaltic waves could be observed through this same area.

A sub-total gastric resection followed by irradiation is the therapy of choice. The prognosis is debatable, although, the authors believe that five years cure is probable. — Franz J. Lust.

Pancreas

COMFORT, M. W., GAMBILL, E. E. AND BAGGENSTOSS, A. H.: *Chronic relapsing pancreatitis.* (Gastroenterology, Vol. 6:4, 239-285 and 5, 376-408, April, May 1946).

On the basis of 29 cases of chronic relapsing pancreatitis without associated disease of the biliary or gastroduodenal tracts of a degree sufficient to influence the clinical picture the following conclusions are drawn:

1) Chronic relapsing pancreatitis appears to represent the summation of repeated attacks of acute interstitial pancreatitis or repeated sublethal attacks of so-called acute hemorrhagic pancreatitis or a combination of the two types of pancreatitis. Interstitial fibrosis and residual necrosis and atrophy are the constant chronic changes. Regions of calcification or stone, pseudo-cysts and abscess are less frequent but striking residua.

2) Chronic relapsing pancreatitis characteristically is a disease of recurring exacerbations separated by short or long intervals of relative clinical quiescence. During the early stages of the disease, the clinician may not be able to demonstrate existence of pathologic physiologic changes, yet the surgeon or the pathologist will be able to demonstrate pathologic changes in the organ. However, later in the course of the disease, the destruction of the pancreas will reach the point where disturbances of internal and external secretion, pancreatic calcification and other sequelae will be demonstrable at all times.

3) The clinical signs are recurring prolonged attacks of severe pains in the upper part of the abdomen, and disturbances of function of the acinar and islet cells and certain sequelae. Disturbances of function may be transitory and mild during the acute episodes before widespread anatomic destruction has occurred. Glycosuria and hyperglycemia, steatorrhea and creatorrhea appear and persist. Pancreatic stones and calcification appears in roentgenograms of the organ and the enlarged organ and cysts may be felt.

4) The clinical signs are due not only to the disease in the pancreas but also to the effect of the disease on neighboring organs. The most striking of these sequelae are obstruction of the common bile duct, jaundice, hepatitis, distention of the gallbladder and obstruction of the duodenum.

5) The treatment of choice is surgical. The results of conservative surgical procedures (internal or external drainage of the biliary tract and pancreatic cysts, pancreolithotomy, or gastro-enterostomy for duodenal obstruction) are sufficiently good to warrant frequent and early use. Radical surgical procedures (partial or total pancreatectomy) may be utilized if the conservative ones have failed and then only for the relief of persistent pains. Medical measures include diet, replacement therapy, drugs for control of pain and measures in case of shock. — Franz J. Lust.

FLINN, L. B., MINNICK, E. AND GAY, D. M.: *Alloxan in the treatment of a case of islet cell carcinoma of the pancreas with liver metastases.* (Arch. Int. Med., Vol. 26, No. 6, June 1947, 936-945).

In a case of insulin-producing islet cell cancer of the pancreas with metastases in the liver, alloxan was used in an attempt to produce a selective necrosis of the malignant tissue, over a period of nine days with a total dosage of 1.16 gms. per kilogram of body weight. No clinical effects were observed attributable to the alloxan, but post-mortem histological examination showed some damage to the liver metastases as compared with biopsy findings taken before alloxan was begun. The effects were therefore less marked than those observed in laboratory animals. Probably larger doses of alloxan should be used in future clinical trials.

Liver and Gallbladder

ABBASY, A. S.: *The efficiency of the Loeffler's methylene blue test as a liver function test.* (Arch. Pe-

diatrics, Vol. 64, No. 5, May 1947, pp. 235-238).

The methylene blue test was tried out extensively on 120 normal and 241 diseased children in an effort to determine hyperbilirubinuria but owing to the fact that "false positives" were given by ammoniacal and concentrated urines as well as in cases receiving penicillin, riboflavine or vitamin B complex, it cannot be relied on to estimate liver function. In cases of manifest jaundice, the methylene blue test could be used as a guide for the progress or regress of the case, but otherwise it has no value.

WATERLOW, J. C.: *Nutritional liver disease in West Indian infants.* (Proc. Roy. Soc. Med., Vol. XL, No. 7, May, 1947, 347-350).

In Trinidad, British Guiana, and Jamaica, the author encountered some enlargement of the liver in ten per cent of unselected infants in the age group six to 18 months. In the clinical cases of "fatty liver disease" the presenting symptoms are vomiting and edema. The edema is of the hypoproteinemic type without albuminuria. The mortality of the disease is high and death appears due to hepatic failure. Analysis of the liver in fatal cases shows a fat content up to 50 per cent of the fresh weight. The bromsulphalein test reveals hepatic impairment during life. It is apparently not an infantile pellagra. The cause of the disease is unknown. About the only valuable fact known is the discovery that increased intake of milk has a curative effect.

PAVEL, I. ET FLORIAN, I.: *Cholecystitis and diabetes.* (Acta G. E. Belgica, March 1947, X, 3, 104-111).

The high incidence of cholecystitis in diabetes is probably not due to the spread of infection from the bile ducts to the pancreas, because such infection usually involves only the head of the pancreas and could therefore not influence body-wide carbohydrate metabolism. Since adiposity predisposes to both cholecystitis and diabetes, we find here a possible link in an etiological chain. Heredity as a predisposing cause to diabetes is probably of more importance than cholecystitis. The authors' arguments are supported by cases and review of the literature.

Ulcer

GRUNISON, K. S., BAYLIN, G. J., TAYLOR, H. M., HESSER, E. H. AND RUNDLES, E. W.: *Transthoracic vagotomy: the effects in 57 patients with peptic ulcer, and the clinical limitations.* (J.A.M.A., Vol. 134, No. 11, July 12, 1947, 925-932).

Healing or quiescence of duodenal or gastric ulcers has followed transthoracic vagotomy alone. Nevertheless, disturbances of gastrointestinal function, including gastric obstruction and retention, have occurred frequently and occasionally have produced serious complications. It seems probable that vagotomy alone should not be used as a standard treatment for all duodenal or gastric ulcers resistant to medical

treatment. Vagotomy may be indicated as a standard treatment in stoma ulcer following subtotal gastric resection.

BERNSTEIN, B. M.: *Histamine in the treatment of peptic ulcer*. (Ann. Int. Med., Vol. 26, No. 6, June 1947, 852-857).

By injecting 0.2 mg. of histamine phosphate daily for 20 days in 75 ulcer patients, the author got prompt relief from pain in four-fifths of the cases and as prompt healing of the ulcers as is obtained by any known form of treatment. Since histamine stimulates the secretion of acid in the stomach, these findings would appear to contradict the thesis that the degree of gastric acidity is important in producing the symptoms and the lesion of ulcer. He believes that the pain of ulcer is vascular and is relieved by histamine which relaxes vascular spasm and increases splanchnic blood supply. The injections of histamine appear to prevent the seasonal recurrences of ulcer symptoms.

SURGERY

TANNER, N. C.: *Transthoracic partial gastrectomy for intussuscepted fibromyoma of fundus of stomach*. (Proc. Roy. Soc. Med., XL, 6, April 1947, 275-276).

Abdominal discomfort after meals led to the gastroscopic diagnosis of a polypus of the gastric fundus. This had ulcerated and bled and the patient required blood transfusion. Achylia was present. Recurrence of pain following transfusion led to an x-ray diagnosis of intussusception of the polypus into the duodenum. A transthoracic transphrenic laparotomy was done, removing the tenth rib. The fundus of the stomach was found to be intussuscepted, the apex of the intussusception being a hard tumor lying in the grossly distended duodenum and was easily reduced. A radical resection was carried out, the upper two-thirds of the stomach, three cm. of esophagus, spleen and neighboring omenta and glands being removed. After closing the cut end of the lower end of the stomach, an "end-in-side" esophago-gastrostomy was performed, the remaining stomach being securely anchored and the diaphragm and chest closed with drainage of the pleural cavity. Recovery was prompt. The tumor proved it to be a non-malignant fibromyoma (a variety of leiomyomata).

SANDERSON, E. R. AND PLAYER, G. S.: *Hour glass stomach*. (Northwest Med., Sept. 1947, 46, 9, 689-691).

An interesting case is described which presented all of the following features — chronic lesser curvature gastric ulcer, hour glass deformity of the stomach secondary to the ulcer, duodenal ulcer with pyloric stenosis and massive gastric hemorrhage from the gastric ulcer. A high gastric resection with antecolic gastrojejunostomy was carried out as an emergency procedure to control massive bleeding with excellent end results. The patient was a woman aged 63 with a history of hemorrhage dating back 36 years.

MARTINSON, L. F., GILLESPIE, S. R. AND HUNTER, A.: *Transthoracic gastrectomy*. (Northwest Med., 46, 9, September 1947, 685-689).

In stressing the importance of early diagnosis of gastric cancer, the authors stress the fact that high percentages (12.3%) of persons with pernicious anemia develop the lesion. Also benign polyps of the stomach may undergo rapid malignant degeneration. Persons with atrophic gastritis develop gastric cancer in about 14 per cent of cases. The patients in these three groups as well as persons with achylia gastrica ought to be subjected to periodic gastroscopic examination as a method of increasing early diagnosis of cancer of the stomach. When a total gastrectomy is to be done the authors prefer the transthoracic approach and they give details on two cases who were operated upon by this route.

BUL. OF THE NAT. SOC. FOR MED. RESEARCH: September-October, 1947.

This journal, devoted to educating the public in favor of the use of animals in experimental studies, carries an editorial by A. J. Carlson in which he praises the victory recently won in a session of the Michigan Legislature. The Michigan law specifically explains the vital part played by animal experimentation in medical research and training and provides for state supervision of such work under the direction of a commission consisting of a humane society official and several deans of medical and veterinary colleges. The text of the law is even less significant than the fact that the biological and medical research institutions in Michigan adopted a positive legislative program six months in advance of the legislative session. They first formulated proposals for a more ideal situation, then contacted the public health committees of the legislature half a year before the sessions were to start. Finally they enlisted the support of a majority of the civic organizations and out-standing individuals in the State. The final step was easy. The lesson of this Michigan model is that public support for a positive program aimed at creating a more ideal situation for biological and medical research is comparatively easy to obtain. In contrast, in most of the remainder of the country, medical research loses public favor by appearing to oppose "humane" standards, however fantastic these may actually be.

METABOLISM AND NUTRITION

COSTA, D. AND CARVALHO, M.: *Vitamin C in 25 Brazilian foods*. (Rev. Brasil de Med., Vol. IV, No. 2, February 1947, pp. 96-98).

The authors attribute disturbed nutritional conditions of Brazil, following the war, to a pronounced deficiency of Vitamin C, due to the wide consumption of orange and guava jam. They report the presence of Vitamin C in mate (Paraguay tea) prepared either with the leaves or with powder, in commercial samples.

FERREIRA, A. J. L. AND VIEIRA, D.: *Estrogenic lipemia: the corrective action of pancreatic extract.* (Rev. Brasil de Med., Vol. IV, No. 2, Feb. 1947, pp. 11-13).

The paper reports experiments performed with pancreatic extracts (obtained by the technic of Dragstedt) in cocks previously and concomitantly treated with estrogens. Injections of the pancreatic extract not only checked, but corrected the changes caused by estrogens in the lipemia of the cocks. Heating the extracts to 100° C. deprives them of this activity. The lipemic levels of normal animals is not appreciably affected by the pancreatic extract. Further researches will determine if the extract is the same as Dragstedt's, who extracted from the pancreas a substance acting upon the fat degenerations of the liver in depancreatized dogs.

LIMA, A. O.: *Allergy to crystallized insulin.* (Rev. Brasil de Med., Vol. IV, No. 3, March 1947, pp. 171-177).

A case of a non-diabetic patient is presented who became allergic to crystallized insulin during a third series of injections. The first series of 20 units daily for two months, given to enable him to gain weight, provoked no reaction. During the second series of injections, urticarial pustules appeared only at the site of injection, and flare ups at the sites of previous injections. Intradermic scarification tests and the passive transfer test were immediately positive for crystalline insulin and negative for other allergenic fractions of pancreatic origin. Dermatological tests were still positive three years after the cessation of treatments.

GOLDBERG, L. AND THORP, J. M.: *A survey of vitamins in African foodstuffs. VI — thiamin, riboflavine and nicotinic acid in sprouted and fermented cereal foods.* (S. Afr. J. Med. Sci., 1946, 11, 177-185).

Kaffir-beer, made from Kaffir-corn, which is the national drink of the Bantu, as well as other malted foods, were investigated for their content of thiamin, riboflavine and nicotinic acid. It was found that germination resulted in a slight loss of thiamin but an increase in nicotinic acid and a high increase in riboflavine, while brewing of Kaffir-beer caused significant increases in all three vitamins, thus more than compensating for losses during germination. The final beer is not merely an aqueous-alcoholic (three per cent alcohol) extract of the vitamins present in the original meal and malt, but contains roughly twice as much thiamin and nicotinic acid and three times as much riboflavine as the original ingredients. It would not be in the dietary interest of the Africans to substitute coffee for Kaffir-beer.

BLOOMBERG, B. M.: *The physiological significance of para-aminobenzoic acid.* (S. Afr. J. Med. Sci., December, 1946, Vol. II, No. 4, 163-171).

By a clever analysis of what is known about the

activities of p-aminobenzoic acid in the animal and bacterial worlds, and by certain experiments conducted on human beings, the author makes out a case against regarding p-aminobenzoic acid as a vitamin. To produce effects on animals, large amounts of the substance have always been required. Intestinal antiseptics (sulfaguanidine) reduced the already small amounts of it which are excreted in the urine. The fact that its only plentiful source is yeast may not mean that it is a part of the vitamin B complex, but rather a by-product of yeast, an organism, which like the bacteria, must have p-aminobenzoic acid as an essential metabolite. The conclusion is that p-aminobenzoic acid exerts its major physiological functions by an indirect stimulating action on the intestinal flora to produce the several vitamins which they have been shown to synthesize and whose importance in the mammalian organism is well established.

SUAREZ, R. M., SPIES, T. D. AND SUAREZ, R. M. JR.: *The use of folic acid in sprue.* (Ann. Int. Med., May 1947, 26, 5, 643-677).

It having been demonstrated by many authors that pernicious anemia, non-tropical sprue, and related macrocytic anemias are promptly relieved by the administration of synthetic folic acid (*Lactobacillus casei* factor), and Spies et al. having reported a remarkable effect on persons suffering from tropical sprue, the University of Cincinnati and the School of Tropical Medicine at San Juan, Puerto Rico commenced a cooperative study of the treatment of tropical sprue with folic acid in November 1945. Fifty cases, 22 of whom were acute full-blown examples, were studied with the endeavor to determine the optimum daily dose; the effect of this dose in the presence of an inadequate diet low in meat, meat products, fish and eggs, from which liver and yeast have been excluded; the effect in the presence of an adequate diet, high in animal proteins and low in fats and carbohydrates; the effect on the glucose tolerance curve and upon the fat content of the stools; the maintenance dose of folic acid; and, finally, whether folic acid can be substituted for parenteral liver extract in the treatment of chronic cases of sprue. Diagnosis rests on the presence of general weakness, diarrhea, glossitis, loss of weight, abdominal distention and severe macrocytic anemia and megaloblastic bone marrow indistinguishable from that of pernicious anemia. X-ray evidence includes the "monlage" sign, or "segmentation" in the small bowel, especially in the jejunum. The studies included elaborate tests on blood pictures, fat, content of stools, stomal punctures, blood chemistry, bile pigment, etc., before, during and after treatment. Briefly, it was found that the adequate daily oral dose of folic acid was 10 mgm. The administration of small daily doses is more effective than 50 times as much given in a single dose. A dose of 20 mgm. of folic acid daily together with an adequate sprue diet gives better results than larger doses accompanied by an inadequate diet. It was the impression of the authors that 2.5 to 5 mg. daily was an adequate maintenance dose for the average case.

HATHERLEY, L. I.: *A case of vitamin C deficiency.* (Brit. Med. Journal, May 17, 1947, 679-680).

A woman of 38 who had been on a restricted diet for six years because of a previous diagnosis of peptic ulcer was found to be suffering from vitamin C deficiency. Severe hematemesis resulted in grave anemia for which many blood transfusions were given without any lasting effect on the anemia. Exploratory laparotomy resulted in finding no sign of a peptic ulcer. Hemoptysis then occurred and a suspicion of vitamin C deficiency led to proof of the same. On vitamin C treatment with the addition of some vitamin K, complete recovery occurred. This is another case which suggests supplementing with vitamins diets of a restricted type if they are long continued.

MISCELLANEOUS

HENNINGSEN, A. K.: *The treatment of hemolytic reactions following blood transfusion.* (Nordisk Med., June 13, 1947, 1341-1344).

The anuria appearing during hemolytic reactions following blood transfusions may be due to blocking of the renal tubules by blood pigment or due to a renal asphyxia caused by toxic breakdown products of hemoglobin, or both. Intensive alkalization is indicated, also re-transfusion with compatible blood. Two cases were saved by these methods but in a third case, alkalization was begun too late. Lumbar pain occurring during transfusion is an indication to abandon the procedure.

BRYAN, S. L.: *Treatment of diabetic coma.* (J. Indiana State Med. Assn., 40, 7, July 1947, 643-645).

The author employs large initial doses of insulin. The initial blood sugar reading in milligrams is an index to the amount of insulin to be given in units in the first 24 hours. Usually 212 units will be needed in the first three hours. Dehydration and lost chlorides are corrected by intravenous normal saline; about 2500-5000 cc. will be required at the rate of 15-20 cc. per minute. Intravenous glucose ought not to be given except where hypoglycemia occurs. Sodium lactate and sodium bicarbonate help clinically but tend to obscure the clinical picture. Gastric lavage is of value. Infection should be looked for and treated if possible. Prevention of coma rests largely on teaching the patient not to discontinue his insulin at times when he cannot eat.

TRETHEWIE, E. R.: *Mustard sensitivity and achlorhydria.* (Med. J. Australia, May 24, 1947, 633-636).

In testing skin sensitivity to mustard on the skins of soldiers, the author found that the two individuals in a group of 12 who were by far the most sensitive to mustard showed achylia. References to the literature are given which suggest that among allergic persons there is a high incidence of achlorhydria. No rationale of the association is attempted, but in assessing a given allergin experimentally on a group of persons, those known to have achylia should be avoided

as their reactions probably will not give representative results.

ALVAREZ, W. C.: *What is the matter with the patient who is always tired?* (Northwest Medicine, Vol. 46, No. 6, June 1947, 437-443).

The "nervous breakdown" is presented as the commonest cause for chronic fatigue. It is to be recognized by apathy and lack of concentration, and may occur in normal persons who work too hard, or with less provocation in those whose heredity predisposes them to it. Insanity equivalents should be kept in mind and looked for. Migraine, constitutional inadequacy, fretting and fussing, encephalitis, thyroid disease, cerebral arteriosclerosis, "little strokes" — all these present material leading to chronic fatigue. The brain itself seems to be the common denominator in all these instances. Superficial laboratory diagnoses of little importance ought not to obscure the basic nervous fatigue that is solely responsible for the patient's plight.

ANTONI, N.: *Polyneuritis.* (Nordisk Med., 23, 24, June 6, 1947, 1285-1293).

One hundred sixty-six cases of polyneuritis are analyzed. Among toxic types are mentioned cases in recent years associated with the administration of the sulfonamides. In 22 per cent of the cases the etiology was obscure. Thirty cases of Guillain-Barre's disease (polyradiculitis) were examined. Biopsy of the *nervous cutan. surae. lat.* is a good diagnostic method. Aneurin was disappointing as a therapeutic agent. Early cases of diabetic polyneuritis react favorably under diabetic management. Brilliant results are obtained in avitaminotic cerebral diseases such as Korsakoff's syndrome.

PASTER, S.: *General aspects of psychosomatic medicine.* (Rev. Gastroenterology, 14, 6, June 1947, 391-401).

A general appraisal and advocacy of the psychosomatic orientation with advice as to caution in psychological approach.

SAVITT, R. A.: *Gastrointestinal disorders in military and civilian life.* (Rev. Gastroenterology, June, 1947, 14, 6, 402-409).

In the army the large number of gastrointestinal disorders poses a serious problem. Once the relationship between emotional and somatic factors was acknowledged, the problem was partially solved by team work between the gastroenterologist and the psychiatrist and the same rule applies in civilian life.

PORTIS, S. A.: *The gastroenterological aspects of psychosomatic medicine.* (Rev. Gastroenterology, June 1947, 14, 6, 409-419).

The psychological accompaniments of ulcer, hypoglycemia in nervous people, gall bladder disease and colonic disease are described. It is suggested that ulcerative colitis might be due to active enzymes hurtled into the colon from a rapidly emptying small bowel. He does not believe that ulcerative colitis can be treated solely by psychological methods.

Gastric Secretory Studies with a Mucin Antacid Mixture *

By
ERWIN M. KAMMERLING, M.D.
and
FREDERICK STEIGMANN, M.D.
CHICAGO, ILLINOIS

THE SUBJECT OF THERAPY in peptic ulcer is one in which medical opinion is much varied. One point on which most are agreed, however, is that reduction of gastric acidity is an important factor in the management of ulcer patients (1). As a result, there are a large and varied number of substances available to the clinician for use as antacid agents (2). This large number is eloquent evidence that no substance has as yet proved to be superior to all others. Among the disadvantages of some of the currently-used antacids are: acid rebound, tendency to alkalosis, too transient neutralization, interference with normal gastric function and unpalatability. For these reasons, search for newer antacids continues. Recently we have studied the antacid properties of a new substance which is a mixture of purified gastric mucin, aluminum hydroxide and magnesium trisilicate. This mixture is supposed to be free of many of the above mentioned disadvantages and, in addition, alleged to be longer acting because it leaves the stomach more slowly.

PROCEDURE

Twenty-five patients with symptomatology and x-ray evidence of ulcer (20 duodenal and 5 gastric) were chosen for this study. The patients were studied from two to five successive days. On the first day, a Levine tube was introduced into the stomach and the gastric contents aspirated at fifteen minute intervals over a period of one hour. Initially, the stomach was completely emptied; later, only a 10 cc. aliquot sample was removed for titration. Before taking a 10 cc. sample, the gastric contents were mixed by alternately aspirating and reinjecting the material several times. After the fourth specimen was obtained, 0.5 mg. (0.5 cc.) of histamine phosphate was injected subcutaneously. Aspirations were continued at fifteen minute intervals until four or five specimens were obtained. The free and total acid values for each specimen were determined by titrating with 0.1 normal NaOH using the standard Topfers and phenolphthalein indicators. The characteristics and admixtures of all specimens were noted. All aspirations and determinations were done by the same person throughout the study.

On the following days, the same procedure was followed with the exception that the patient was

given an antacid preparation following the fourth aspiration and just preceding the histamine injection. The following antacids were studied on subsequent days:

a. Mucin-antacid mixture — two tablets, or one teaspoonful of powder.

b. Sippy tablets — two — gr x calcium carbonate, gr xxx Sodium bicarbonate, or

Sippy powder — one teaspoonful (calcium carbonate, one part; sodium bicarbonate, two parts).

c. Amphogel — two tablets.

Most of the cases were tested as above. A smaller number were tested only with the new antacid mixture.

We were also interested in noting whether the mode of administration of this antacid mixture would influence its effect on gastric acidity. Therefore, on one day the patients were instructed to chew two tablets thoroughly before swallowing and on the second day, to allow them to dissolve by sucking them.

During the test period, which lasted two hours, the patients were allowed to converse, read "bland" literature and walk about at intervals. Smoking was prohibited immediately preceding and during the test period as was discussion of such stimulating subjects as politics, war possibility, etc. Patients were asked not to swallow any saliva or post-nasal secretions.

RESULTS

The antacids used in this study were evaluated on the basis of their relative effect on gastric acidity, on the duration of the antacid effect, the degree of rebound and on the physical characteristics of the aspirated juice. The height of the response to histamine was compared to the initial (pre-histamine) values which varied in many patients from day to day. In 92% of the cases, all antacids used showed an effect on gastric acidity. The different antacid preparations used varied somewhat in their effect. In 55% of the cases, the new antacid mixture (Table I) produced a lower acidity than the other substances used (Figure 1); 18% showed the effect to be similar (Figure 2); and in the remaining 27%, the new antacid mixture was less effective (Figure 3). After the administration of the new mixture and amphogel tablets, respectively, the acid curves are almost identical although the base line of the new mixture curve (before histamine and antacid) was about 14 units higher than the other (Figure 4). After administration of the new substance and Sippy tablets respectively the acidity curves follow each other closely, although the pre-histamine level of the Sippy curve is about 14 units higher than the other (Figure 5).

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*Aided by a grant from the Research Division of the Harrower Laboratories, Inc., Glendale, California.

TABLE I

Free Acid Levels During the Fasting Period and After the Injection of Histamine Alone and with the Simultaneous Oral Administration of an Antacid Substance

Fasting Specimens				Antacid Tested	Specimen After Histamine Injection — With and Without Antacid Administration				
1	2	3	4		15 Min.	20 Min.	45 Min.	60 Min.	75 Min.
29	35	36	39	Histamine only	65	76	67	63	61
32	36	35	35	Mucin-Antacid Mixture* Tablets	20	36	47	49	41
32	36	39	44	Histamine only	56	65	61	57	
18	35	39	38	Mucin-Antacid Mixture Powder	4	25	36	42	58
26	30	38	42	Histamine only	56	66	63	58	
27	35	44	43	Sippy Powders	9	30	35	43	64
42	53	52	56	Histamine only	73	84	80	77	77
35	48	42	39	Aluminum Hydroxide** Tablets	27	53	60	63	63

*Prepared by Harrower Laboratories, Inc., Glendale, California, under the name of MUCOTIN.

**Amphogel Tablets were used.

There was greater antacid response when the tablets were chewed than when sucked (Figure 6).

In 70% of the cases, gastric aspiration yielded milky fluid from fifteen to forty-five minutes longer following the ingestion of the new antacid mixture.

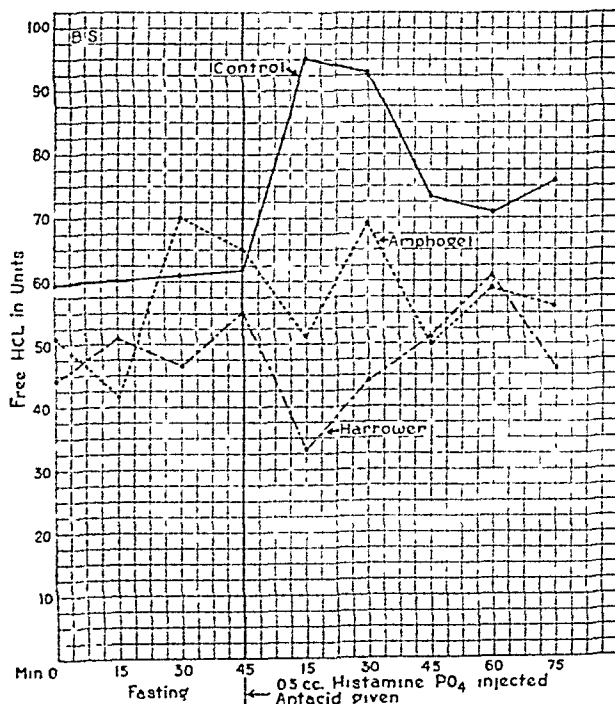


Figure 1 — Lower free acidity following the new mucin-antacid mixture (Harrower) than after amphogel.

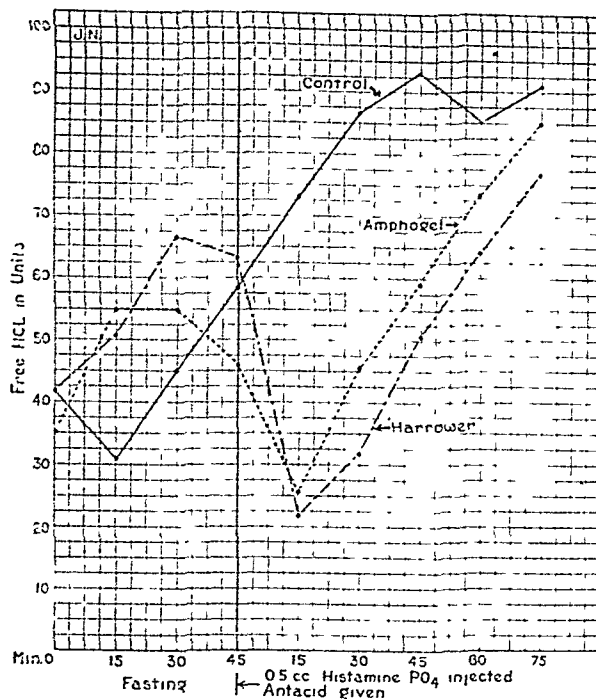


Figure 2 — Equal decrease in acidity following the new mucin-antacid mixture (Harrower) and amphogel.

Apart from this observation, there seemed to be no consistent difference in the physical appearance of the specimens following the various antacids used.

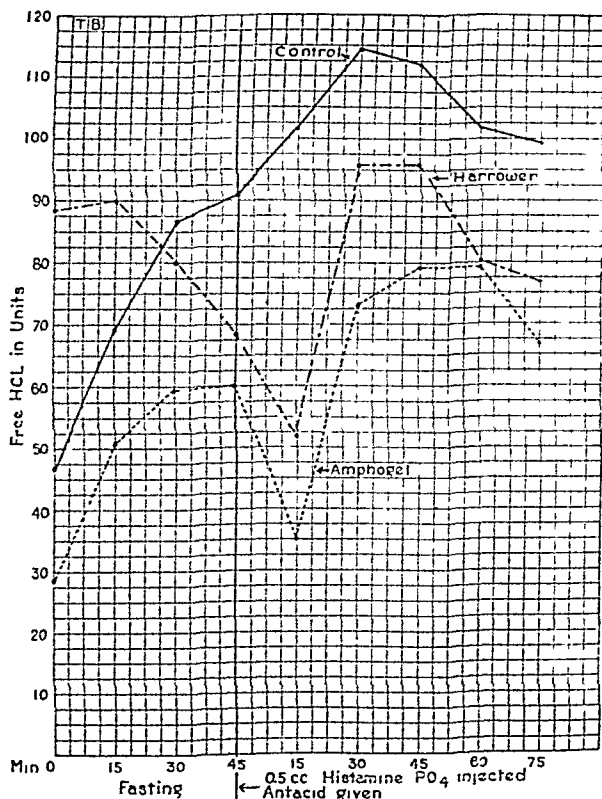


Figure 3 — Graph showing lower acidity following after amphogel than after the mucin-antacid mixture (Harrower)

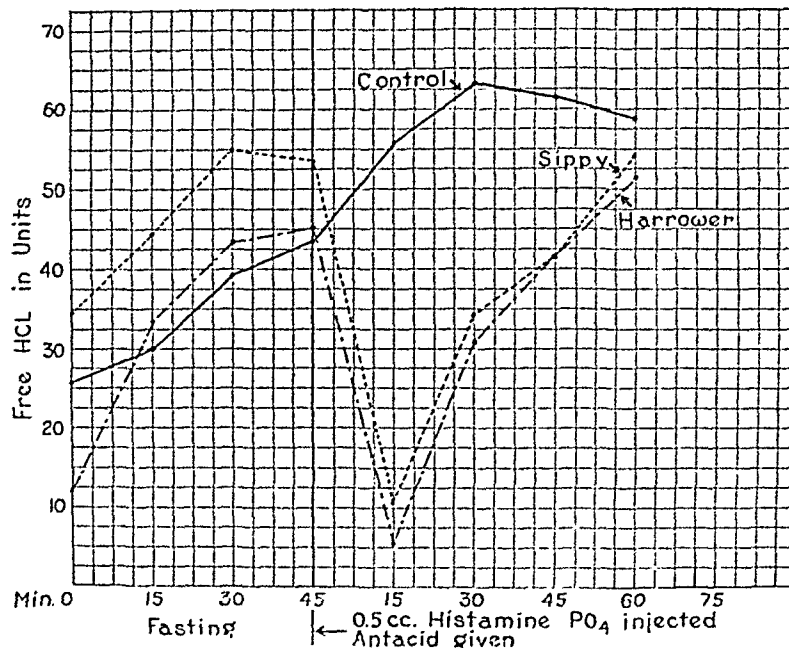


Figure 4 — Composite graph showing lowering of acidity after both Sippy tablets and the new mucin-antacid mixture (Harrower) tablets.

The presence of mucoid material which made the samples more viscid did not vary consistently with the antacid used. Similarly, the presence and quantity of bile could not be correlated with any particular substance.

DISCUSSION

Because of the small number of cases, the data are not sufficiently conclusive to permit a statistical analysis. From this preliminary observation, however, it would appear that this new mixture was more effective

than the other substances in a larger number of cases. That this new substance remains longer in the stomach is indicated by the recovery by gastric aspiration of a milky sample from fifteen to forty-five minutes longer than following ingestion of the other antacids. This observation is substantiated by x-ray studies which showed that barium remained in the stomach longer when it was mixed with this mucin preparation than with the others (Sippy and amphogel) (3). Similarly, gastroscopic observation thirty to forty-five minutes after ingestion of these three test substances revealed the presence of significant

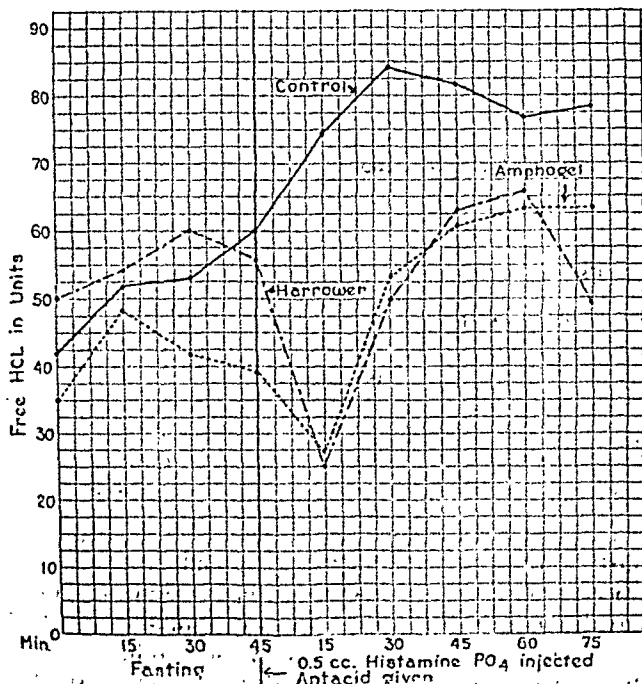


Figure 5 — Composite graph showing lowering of acidity after both amphogel and the mucin-antacid mixture (Harrower) tablets.

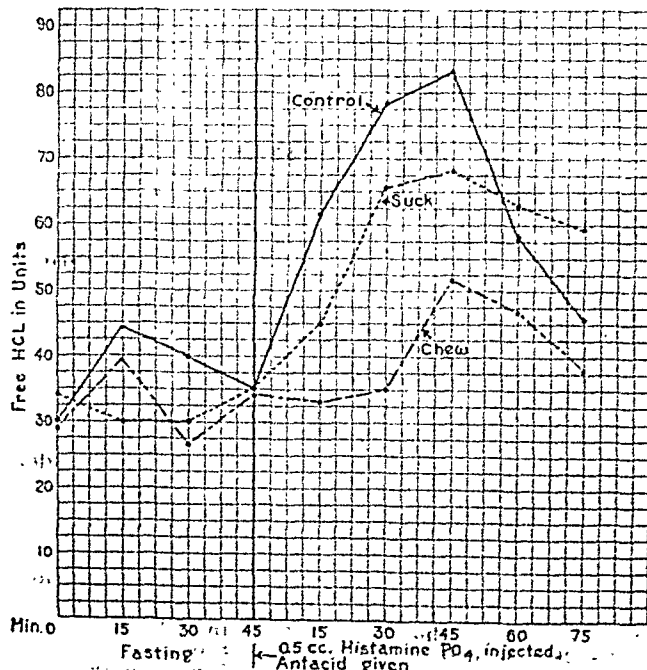


Figure 6 — Graph showing the more marked decrease in acidity after chewing than after sucking of the mucin-antacid mixture (Harrower) tablets.

amounts of mucin preparation uniformly spread while the other substances were scarcely present and, if present, were in patches (3). That the effects of the mucin preparation were more marked when chewed than when swallowed is in accord with previous observations on other substances concerning the greater chemical effectiveness of a finely divided substance than of a coarser one, as a tablet.

Clinical observations concerning the effect of this new antacid preparation are at present under way. The length of time of observation and the number of cases studied are still not sufficiently large enough for a conclusive statement. It appears, however, from the observations thus far that the clinical results seem to run parallel with the observation on the antacid effects.

SUMMARY AND CONCLUSION

A new antacid — consisting of a mixture of mucin, aluminum hydroxide, and magnesium trisilicate has been compared with other currently used antacids (Sippy or amphogel) concerning its effect on gastric acidity.

It appeared to produce a decreased acidity in a higher percentage of cases and this antacid effect seemed to last longer than with other substances.

There appeared to be less rebound of the acidity with this substance.

It is palatable, easily taken by the patients and has a better antacid effect when chewed carefully before swallowing it.

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Ulcerative Colitis

An Evaluation of the Etiology, Symptomatology and Therapy

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IDIOPATHIC OR NONSPECIFIC ulcerative colitis is a chronic disease characterized by a suppurative and necrotizing inflammation confined to the large bowel.

As a rule it begins in the recto-sigmoid and the distal portion of the descending colon. In milder forms (20-30% of the cases) it is confined to this region. With increased severity and continued activity

it spreads to the upper part of the descending, the transverse and ascending colon, may involve the cecum, and, in rare cases, even the terminal ileum. The disease may also involve one or more segments without affecting the rectum. This latter type of disease is known as segmental or, if limited to the proximal large bowel, as right sided ulcerative colitis.

The morbid anatomy is characteristic. The process starts with an acute inflammation and edema of the mucosa, followed at times by necrosis and sloughing, and leading to the formation of minute and later larger ulcers. These ulcers vary in depth, they are superficial and shallow in the beginning, involving little more than the mucosa. Later they penetrate deeper, denuding and exposing the submucosa. The

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mucosa and submucosa become infiltrated and thickened by inflammatory tissue, while in late stages hyperplasia of isolated areas of mucosa leads to the formation of adenomatous tissue and polyps. Finally, the disease process results in scarring, narrowing, fibrosis, and a marked shortening of the involved colon.

Ulcerative colitis is a disease of world-wide distribution, with apparent increase in frequency. It is difficult to say whether this increase is an actual one, or is only due to our greater awareness of the disease and improved diagnostic methods. It occurs in both sexes and at all ages, though it is particularly common in the second, third, and fourth decades of life. It also occurs at both extremes of life. Familial incidence has been reported on several occasions, but there is no evidence that contagious or hereditary factors are of any real importance.

In considering the possible etiology of the disease, we must first differentiate between forms of ulcerative colitis of a specific nature and those of so-called idiopathic ulcerative colitis, which are of unknown etiology. In the former, the colitis may be due to bacillary, amebic, tuberculous infection, balantidium coli, and virus of lymphogranuloma venereum. In the idiopathic forms no systemic disease can be found, and no definite infectious agents have been established, in spite of the fact that the appearance of the lesions and the systemic reactions suggest infection. It is not surprising, therefore, that the attention of many investigators of the disease has been primarily focused upon the normal and abnormal bacterial flora of the bowel, and that almost every organism isolated from the feces has been thoroughly investigated.

Hurst, and later Felsen, drawing conclusions from follow-ups of bacillary dysentery cases, suggested an attractive hypothesis that the disease process is initiated by a specific bacillary infection and then is maintained as a non-contagious form by other non-pathogenic inhabitants of the colon. Although there is definite proof that this may be true in a certain percentage of cases, this concept surely cannot be applied to all cases.

Since 1924 Bagen has advocated a diplobacillus as a prominent etiologic factor in a group of cases which he calls thrombo-ulcerative colitis. Bagen was able to produce ulcerations and hemorrhages in the colon of rabbits by injecting the diplobacillus cultured from ulcers of the large intestine of patients. Paulsen, Rafsky and Maubheim, Torrey and Montu, after exhaustive bacteriological and experimental studies, came to the conclusion that the Bagen organism is only a variant of a heterogeneous group of streptococci, which may act as a secondary invader, but, which are not capable of primarily producing ulcerative colitis.

Whether the *Bacillus necrophorus* found by Dragstedt, Dock and Kasper in many of their cases is an etiologic agent is not settled, and is awaiting further investigation. The same holds true for the etiologic role of viruses, fungi, pancreatic enzymes, and food allergy. There is no good evidence that viruses (Mones and Sanjuan) are contributory etiologic factors, or that

fungi may produce the disease, although infection with *histoplasma capsulatum* has been reported to produce ulceration of the colon (Henderson). Parke, Ward and Needles suggested that ulcerative colitis may be due primarily to large amounts of active pancreatic enzymes entering the colon. This would produce a primary increase of oral intestinal motility and a considerable susceptibility of the colonic mucosa to these enzymes, which is not proven and difficult to assume. There is no question that patients with ulcerative colitis, like any other group, may be sensitive to different foods, but we should not forget that in allergic persons, the occurrence of diarrhea is as common as that of constipation. Should allergy be an important etiologic factor as suggested by Andreessen, it is difficult to understand why in protracted or fulminating cases in whom nutrition is maintained, often for many days, by the intravenous route, the disease does not abate rapidly. In spite of this, the favorable results of Andreessen are remarkable and should be controlled on a large number of cases. Constitutional, metabolic, and endocrine disorders, deficient diets, and deficient vitamin A or B contents of the diet may have some importance as cumulative factors, but there is no convincing proof of their importance in initiating the disease.

The concept of a psychogenic cause is based on clinical and experimental evidence. There is no question that recurrences or exacerbations of the disease can often be traced to emotional disturbances. Many patients with this disease have very definite personality changes, but whether this is propter hoc or post hoc is difficult to say. A disease of the character and duration of ulcerative colitis, with all of its social, professional, and economic disturbances can have a profound influence even upon a most normal individual. There is no doubt in my mind that psychogenic factors, whether propter hoc or post hoc, and abnormalities in nervous impulses via the sympathetic and parasympathetic tracts, may aggravate and perpetuate the disease, but whether they are able to initiate it, is unproven and doubtful.

As long as there is no better explanation, we may say in conclusion, that idiopathic ulcerative colitis is a condition in which the colonic mucosa is primarily damaged by some unknown factors, and that it loses its natural protective ability against its own saprophytic inhabitants. These microorganisms, harmless under normal circumstances, invade the functionally impaired mucosa and produce the known pathological changes. The analogy with the unknown factor which erodes the gastric mucosa, loss its protective ability against acid pepsin in ulcer diathesis is striking, likewise the implication of psychic factors in both diseases are quite similar.

The clinical features and symptoms are so well known to warrant much detail. They vary very considerably with the type of the disease, whether it be acute or chronic in character.

The acute form may be mild or fulminating and associated with a severe toxemia. It may continue for weeks or months and it may end fatally or relieve.

Bouts of acute attacks may occur at any time, but they are especially frequent after upper respiratory infections, emotional disturbances, and dietetic indiscretion. Some of the patients may continue for years in a fair condition, some may eventually lose their symptoms and lesions, while others may be semi-invalids or invalids for life.

The onset may be insidious and not accompanied by diarrhea, the first symptom being the appearance of bloody mucus on the surface of the stool. In the severe acute cases a diarrhea, which may change to practically continuous evacuations of mucus and blood, is the outstanding symptom. The colicky abdominal pain is diffuse and is associated with an urge for defecation. The pain is relieved temporarily by a bowel evacuation, but is often followed by renewed tenesmus.

Anorexia, epigastric distress, nausea, and vomiting are seen in the acute stage but they may be entirely absent in the mild or protracted cases. Weight loss, weakness, temperature rise, and anemia, depend upon the acuteness of the disease and the severity of the systemic toxemia.

Complications seen in the course of the disease may be of local, colonic, or systemic nature. The most common colonic complications are massive hemorrhages, strictures, obstruction, perforation with peritonitis, fistula formation, and polyposis of the colon. Whether the incidence of carcinoma is greater in the colon with ulcerative colitis than in the normal colon is not yet established, but the pathological relationship of colonic polyposis and carcinoma is suggestive.

The most common systemic complications are nutritional deficiencies, arthritis, and skin lesions. In the acute forms of the disease with profuse bloody diarrhea, high temperatures, perspiration, and complete anorexia, dehydration with electrolyte and blood loss may become an outstanding feature. In chronic forms, multiple vitamin deficiencies, anemia, hypoproteinemia, hypocalcemia, and diminished food utilization are factors which, when not corrected, contribute to a rapid downhill course of the patient.

Arthritis, involving many joints, is not an uncommon complication, and may develop into a crippling disease. It is probably the expression of an allergic response of the synovia to circulating toxins, and it may be due in part to the severe demineralization of the bones seen in chronically ill and bedridden patients. With the subsidence or improvement of the disease, or following colectomy, the arthritis may disappear completely.

Necrotizing skin lesions developing around fistulous tracts, ileostomies, or at other parts of the body, are of grave significance, difficult to treat, and are probably the result of toxemia, avitaminosis, and lowered tissue resistance.

Generally, the diagnosis of ulcerative colitis is not difficult. History, symptoms, proctosigmoidoscopic and x-ray examinations, are characteristic, and in the majority of cases there is no doubt as to the nature of the disease.

When the rectum is involved, as it is in most of the cases, the diagnosis can be made by proctoscopy;

the mucosa is hyperemic, edematous, and bleeds easily after swabbing. Ulcerations, when present, are usually small and shallow. In advanced cases these changes are more pronounced. The mucosa has a beefy-red, granular appearance, and is covered by patches of mucopurulent exudate or by a thick diphtheria-like membrane. The lumen of the rectum may be tubular and narrowed, while hyperplastic polypoid areas are seen occasionally.

The x-ray changes that one sees depend upon the site and extent of the pathological changes, and the irritability of the involved area. It is well to keep in mind that in acute, even fulminating cases, the findings in the early stages may be minimal and limited to a fuzzy appearance of the bowel contours, although proctoscopic examination may reveal a severe picture. With the advance of the disease the distortion of the mucosal pattern, loss of haustrations, shortening, and narrowing of the gut are prominent features.

Differential diagnosis must exclude amebic and bacillary dysentery, tuberculous enterocolitis, balantidium coli infection and, more rarely, lymphopathia venerea. These conditions may more or less duplicate the symptoms and pathological findings of idiopathic ulcerative colitis. Amebic colitis involving the rectum may be identified proctoscopically by its sharply punched out ulcers, surrounded by a red halo, and separated by islands of normal mucosa. Frequent stool examinations and cultures of fresh specimens in a reliable laboratory and, when stool examinations are negative, the newly advocated complement fixation test, may help to establish or rule out an amebic infection.

Most observers agree that it is very difficult, if not impossible, to differentiate proctoscopically acute and chronic bacillary dysentery from idiopathic ulcerative colitis. Stool examinations for dysentery bacilli are positive in the early stages of the disease only, and rarely in the later stages. The agglutination tests are reliable in the Shiga type of infection, but less dependable in the Flexner or Sonne-Duval types. They may be highly positive, however, in normal sera, due to cross agglutination with related bacteria. It is, therefore, probable, as has been suggested by Hurst and lately by Felsen and Winkelstein, that an unknown number of cases of ulcerative colitis are the aftermath of a previous dysenteric infection.

Tuberculous ileocolitis may be ruled out by stool examination for tubercle bacilli, and by a guinea pig inoculation test.

Lymphogranuloma venerea may at times produce a proctoscopic picture similar to that of idiopathic ulcerative colitis. However, stricture formation in the rectum is not seen in ulcerative colitis, and a positive Frey test may help differentiate these conditions.

The therapy of idiopathic ulcerative colitis is not very satisfactory, due to the lack of specific treatment. The multiplicity of therapeutic agents which have been advised and praised for their good results make it clear that no real cure is yet at hand. The writer is convinced that the treatment of ulcerative colitis is primarily a medical problem in which patience, optimism, and perseverance on the part of the physician

and the patient are important factors in the management of the condition.

Hardy and Bulmer very aptly stated years ago that "there are very few diseases in which patients can reach such a state of emaciation and exhaustion and yet recover."

In acute, subacute, and chronic cases with exacerbations, prolonged bed rest and competent nursing care are indispensable. Medical care must be directed toward local and constitutional factors.

The functions of the small intestine being nearly normal, there is no excuse for withholding from these often poorly nourished and dehydrated patients a smooth, well-balanced, low residue diet, rich in protein, carbohydrates and vitamins. Attention should be given to individual idiosyncrasies to food and to the often encountered intolerance to milk.

In severely ill, toxic cases and in those who cannot be fed orally, small blood transfusions (250-300 cc.) repeated every two to three days, intravenous fluids like glucose, saline and amino acids, may help tide these patients over a critical period. Vitamins of the B group, daily intramuscular injections of crude liver extract, Vitamins C and K, calcium and iron must be supplied in order to prevent deficiencies which inevitably develop with protracted diarrheas, severe toxemia, and fever.

As a rule, I give every patient with ulcerative colitis the benefit of antiamebic therapy because I have had good results in cases that proved to have amebic infection, in spite of repeated negative results of stool examinations. Caution is advised with the use of emetine in general, and particularly in fulminating cases.

Sulfonamides, such as sulfadiazine, sulfathiazole, sulfasuxidine, sulfaguanidine, and lately sulfathalidine, are used extensively with results reported as good by many. In my own experience and in that of others the results with these drugs have not been encouraging. Lately, Major has reported encouraging results with two new compounds, nisulfazole and nisulfadine, but confirmation in a large series of cases, observed over a long period of time, is necessary.

The combined use of sulfonamides and penicillin and, according to the few available reports, the use of streptomycin have not been able to improve the results of the anti-infectious therapy. It seems to me that all attempts at *sterilisatio magna* of the colon have failed us up to the present. In spite of this, patients should be given the benefit of sulfonamides, especially in acute or fulminating cases, in which often a beneficial effect on fever and toxemia is obtained. Unfortunately, this effect is sometimes only transitory. The use of sulfonamides has proven to be of no value in any chronic cases.

Autogenous or non-specific vaccine, Bargen serum, and the non-specific bacillus coli serum advocated by Winkelstein and Schwartzman have been and are still used in the treatment of the disease. There is no doubt that benefit can be derived in some cases from any of these therapeutic measures, but this benefit is unquestionably of a non-specific nature. Not long ago,

I obtained very good results in a moderately severe case with the use of typhoid vaccine, after all other therapeutic measures had failed.

The treatment of the diarrhea, the most distressing symptom of ulcerative colitis, is not very satisfactory. Chalk, Kaolin, Kaomagma, Zymenol, Pectin, Consyl, etc., are commonly used drugs, that are of very limited value.

The use of morphine should be condemned for two reasons. Firstly, in spite of relieving pain it increases the spasm of the already irritable colon, and secondly, it may be habit forming in a disease with such a protracted course. Demerol in 100 mgm. doses is preferred, for it is also an antispasmodic and, while it may be habit forming, it does not produce euphoria which is the main stimulus for habituation. The use of Demerol should be limited to the relief of severe pain. The constant discomfort produced by the irritability of the colon, namely spasm and rectal tenesmus, is best treated by belladonna and the atropine-papaverine drugs. Pavatrine or trasentine in combination with phenobarbital are very beneficial and should be used routinely.

Last but not least, psychotherapy as commonly used at the bedside, should be extensively applied to every patient suffering from ulcerative colitis. Psychological survey, a friendly, encouraging and hopeful attitude, combined with a genuine interest in the patient's problems can be of great therapeutic value. In selected chronic cases the help of a psychiatrist is desirable and beneficial.

The question of surgery in idiopathic ulcerative colitis is controversial, and the trend among gastroenterologists is now towards conservative medical therapy. I am not so sure that cases in which an ileostomy has been claimed to have been life-saving, would not have recovered without this intervention. Whether the installation of an ileostomy puts the large bowel at functional rest, as it is assumed, has no experimental confirmation. I cannot see how by this operation the motility, secretion, and the reflex activity of the colon can be abolished. Furthermore, psychogenic and emotional reactions may be aggravated easily by a surgical procedure which involves a great many uncomfortable and distasteful psychic and physical traumas.

Absolute indications for surgery are perforation, severe obstruction, perianal and perirectal infections which may block or sidetrack the fecal current, and carcinoma. In cases of regional, segmental, or right-sided ulcerative colitis without rectal involvement, surgery may be very gratifying in properly selected cases. The indications for surgery in these cases are not always absolute, and some may do well on medical management.

With regard to advising surgery, the most disputed group is that with the continuous type of ulcerative colitis who are seemingly intractable medically, who have a severe arthritis and other systemic complications, and who fail to respond to adequate therapy. Should such cases be operated upon? I am unable to give a satisfactory answer but I stress conservatism. I have seen cases upon whom the suggested operation

has been performed and who either died or continued a very unsatisfactory life. I remember other patients who refused my advice for surgery and then experienced a remission of several years duration, after I had lost all hope for their improvement. Unfortunately, there are no definite criteria at the present time, upon which a decision for or against surgery can be based, and as long as this situation prevails the medical man will have to take the blame for not referring these patients to surgery in time.

Bargen, Lindahl and colleagues have reviewed the results of 185 ileostomies performed on 5.5% of their patients with ulcerative colitis. 29.7% of the patients lived less than six months and 26% died shortly after six months, an overall mortality of 43%. Bargen noticed definite progression of the disease and its complications in all but 37 of the remaining pa-

tients, with 11 deaths from 30 cases with subsequent colectomies.

Should the decision be in favor of surgery, two things seem to be definitely established today. Firstly, that surgery should never be done in the acute or fulminating stage because of the very high mortality. Secondly, when an ileostomy has been performed in a case with a severely damaged colon, it should be followed by a colectomy, i.e., an ileostomy should never be closed.

The results of medical therapy of idiopathic ulcerative colitis have shown remarkable improvement in the last ten to fifteen years, with a high mortality rate remaining only in the acute and fulminating cases. I feel that the disease process in this latter group is so severe that survival is rare, in spite of the best medical or surgical care.

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The Consideration for Surgery in Ulcerative Colitis

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AFTER MANY YEARS of extensive experimental and clinical research, the undoubted causal factor in ulcerative colitis has not been determined. Some specific infections, such as bacillary dysentery, amoebic dysentery and lymphopathia venereum, may produce segmental or diffuse ulceration and other pathological changes in the colon wall similar to ulcerative colitis, but we do not have evidence to support the contention that any one of these specific infections is always the forerunner of so-called idiopathic ulcerative colitis. Other specific organisms have been accused of this grave misdemeanor but none have withstood the repeated test of attempted substantiation. Disturbed states of the digestive juices, dietary deficiency, vitamin deficiency, psychosomatic influences, autonomic nervous system disturbances, allergies, vascular and lymph changes, and focal infection have been promulgated as the etiological factor or factors. At the present time, one can assume that some colon wall barrier or defense mechanism momentarily breaks down and a synergistic phenomenon composite of several of the factors just mentioned, including infection, establishes the condition. Infection and a vicious circle of adverse conditions in a

bacteria-bathed and injured colon wall favor chronicity. Emotional and psychic disturbances may exacerbate the condition by their effect on the motor and secretory mechanisms of the gastrointestinal tract, but it is difficult to convince surgeons that the psychosomatic factor can be the initial cause of tissue breakdown or necrotism.

PATHOLOGIC ANATOMY

This inflammatory condition begins in the rectum in ninety per cent of the cases. Early in the disease, the mucosa is hyperemic, with or without edema. Shallow erosions develop at the sites of minute abscesses, edema becomes more marked and the inflammatory reaction becomes more acute, with an angry red appearance, frequently mottled. The ulcerations become more prominent and deeper, with the long axis quite likely to be arranged longitudinally. A mucopurulent, blood tinged exudate is present or small blood clots may be distributed over the ulcerating area. The ulcers coalesce as denudation of the mucosal layer continues, causing a granular appearance, and varying degrees of stricture and scarring ensue. Between ulcers, proliferative hyperplastic tissue and polypoid development makes its appearance. All layers of the bowel wall become involved and if the peritoneal cavity is opened, the serosa appears

edematous and injected. In the early and acute phase, the caliber of the bowel may be large, but later it usually becomes contracted. The disease tends to spread throughout the colon although segmental types may occur with involvement of only a section of the colon and with or without later involvement of the rectum.

CLINICAL PICTURE

Cave (5, 6, 7) refers to four types of the disease, which is a good clinical classification — namely 1) mild cases, at least temporarily arrested and perhaps cured by medical management alone; 2) chronic with remissions; 3) chronic, continuous; 4) acute, fulminating, frequently fatal.

The onset may simulate acute enteritis with frequent loose stools and abdominal cramps, accompanied by varying degrees of mucous or bloody rectal discharge with or without purulent exudate. In the acute, fulminating type, the patient has almost continuous liquid evacuations. Fecal material is minimal, and the discharge consists almost entirely of mucus, pus and blood. With subsidence of the acute phase, stools may continue to be loose and frequent and urgency is a common symptom. Periods of constipation may occur only to be followed in most cases by a bout of stool frequency. Abdominal distress and colic are common complaints, and these frequently rush the patient to a toilet where he expels some gas, a little bloody mucus, or minimal watery fecal material, usually with at least momentary relief from the rectal tenesmus.

The patient may have no increase of temperature, may carry a low grade temperature, or a severe septic temperature may be present. A systemic toxemia is usually associated with some rise in temperature, and in these cases there is usually loss of weight and strength, anemia, and nutritional disturbances. In the chronic state, many patients maintain their weight and show very few or no effects of a chronic infection. Any and all complications of infection with its secondary manifestations may occur.

DIAGNOSIS

The physical examination may reveal nothing of significance except some tenderness along the colon and not infrequently this is minimal. With a suspicious history, one must immediately make a rectoscopic examination and he will usually be directly rewarded by being able to prove or disprove the presence of ulcerative colitis. The appearance of the bowel wall varies as heretofore described, and in practically every case whether in the acute, chronic or subsiding stage, the rectal wall bleeds easily. In the acute, fulminating form or advanced chronic stage, narrowing may be marked, and digital examination may warn the examiner that rectoscopic examination will be difficult. At times it is almost impossible to insert the average size proctoscope. In other cases, pseudo-polyp formation, resulting from the hyperplasia, may make one suspicious of polyposis of the colon. However, the pseudo-polyps are softer, the surfaces are irregular, and the

granular appearance of the mucosa between the polyps distinguishes the condition. Warm stool examination should be done to exclude amoebic ulceration, and it is of greater value to obtain a specimen from the ulcerated area through the proctoscope.

Second in importance to the proctoscopic examination in the diagnosis is the roentgen examination. Barium enema studies usually offer some evidence of the extent of the disease although one cannot exclude ulcerative colitis by a negative x-ray report. X-ray examination may be of particular value in segmental ulcerative colitis. Usually the affected area reveals no haustrations and a fuzzy margin. However, mucus adhering to the mucosal layer or distortions of the muscularis mucosa may give a similar picture. Likewise lack of haustration may mean only functional changes of the colon. True narrowing with fibrosis and shortening, especially the "gas-pipe" appearance, are most significant. Barium-air contrast enemas are more diagnostic for polyposis. Large polyps are usually of the congenital type and one can usually differentiate the two types without difficulty by proctoscopic examination.

Every patient with recurrent or protracted diarrhea, especially with the history of passing blood, must have malignancy and amoebic dysentery ruled out. If these are excluded, the chances are that idiopathic ulcerative colitis exists.

THERAPY

It is my belief that the treatment for ulcerative colitis is primarily medical, and that about ninety per cent of the cases will respond to it to a greater or lesser degree. Usually these patients are not cured and relapses, either mild or severe, may be expected. With peptic ulcer, non-surgical management keeps the condition under control in about eighty per cent of the cases. Relapses occur, but surgery is not indicated unless these are of a complicating nature. However, surgery for peptic ulcer is not so devastating as the establishment of an ileostomy, and mere relapse, unless frequently incapacitating and complicating, is not an indication for surgery in ulcerative colitis. Various specific agents have been advocated for ulcerative colitis, but none have proven sufficiently successful to be universally adopted. The many treatments which have been advocated and the frequent introduction of new regimes are the existing proof of the inadequacy.

Those who manifest an interest in the surgery for ulcerative colitis should be alert to all forms of proper medical management of this condition. A surgeon should be able to distinguish whether the case presented to him for surgery has had all the advantages of detailed medical management before committing himself as to the advisability of surgery. The interest, ability and pessimism of medical men or internists in the management of this disease vary considerably. To recommend ileostomy, colostomy, or resection with or without anastomosis, and usually ileostomy is the recommended procedure, is a major decision of great significance to the patient. The surgeon should have

crystallized in his own mind what constitutes adequate medical management.

A diet low in residue and high in proteins and carbohydrates is universally accepted. The calorie intake should be high. If the patient is too ill or fails to eat, supplements should be added, especially the protein hydrolysates, to prevent or correct a hypoproteinemia. Some direct that insulin be given daily to stimulate the appetite. Attention must be given to water and electrolyte balances, and a high vitamin intake must be maintained. This is particularly true when stools are frequent and copious. Mackie, Eddy and Mills (11) have admirably detailed the vitamin requirements for patients with ulcerative colitis.

Symptomatic treatment directed toward minimizing intestinal spasm and frequency of stools should be emphasized more frequently. Many times these are the conditions for which the patient seeks relief, rather than the effects of a devastating infection. Atropine, belladonna or other anti-spasmodics are indicated routinely. A mixture of equal parts of milk of bismuth and paregoric in one or two drachm doses after every second bowel movement of the 24 hours seems to be a practical measure. In addition, kaolin in some form, with or without pectin, may be used.

The poorly absorbable sulfonamides are of some value in the management of some cases, but a critical analysis fails to supply convincing proof of many actual cures. Sulfathaladine appears to be most widely used at this time, and is usually administered in 1 1/2 gram doses four times daily over a period of two or more months. In some cases, the temporary results at least are quite striking. Penicillin and streptomycin have not given encouraging results. In fulminating cases, one should certainly use sulfonamides and penicillin until we have definite proof that they are of no value.

Rectal instillations have been decried the last few years, but I do not believe one can deny the fact that before the advent of the newer antibiotics, certain drugs per rectum did seem to be effective in some cases. One might argue that the supportive treatment was responsible for the improvement of the patient, but the same argument will hold with any of the newer treatments. Gentian violet and acriflavine by mouth and per rectum were used rather widely at one time, and certainly are still worthy of trial in some cases. Instillation of kaomagma has also been advocated. Cod liver oil instillations (2), one ounce per rectum once a day or every other day for a period of several weeks, have certainly been helpful in some cases, and should be tried. The principle of cod liver oil per rectum is the same as for other open, sluggishly healing surfaces plus the possibility of some absorption taking place.

The existing anemia must be corrected and blood transfusions frequently give these patients a tremendous boost in their general condition. Plasma and intravenous protein hydrolysate are used to further correct the hypoproteinemia. Blood plasma also helps to overcome any existing or threatening acidosis.

At one time, there was a wave of enthusiasm for

the use of vaccines and sera of various types, but only a few have continued to use this type of therapy. Fever therapy and foreign protein therapy have also been tried.

The psychiatric phase has been studied and some are so enthusiastic as to believe that with the term "psychosomatic," the panacea has finally been discovered. It is true that these patients many times develop emotional disturbances and that psychic factors may exacerbate an attack, but it is difficult for the surgeon to accept the theory that psychic influences can cause tissue to necrotize and ulcerate. This statement is made irrespective of existing theories about some phases of peptic ulceration.

INDICATIONS FOR SURGERY

Not infrequently one hears or reads the statement that doctors have too long relegated the treatment of ulcerative colitis to a medical regimen and consequently the patient arrives for surgery in a miserable condition. It is my reaction that it is far better to have a few patients arrive too late for surgery than to subject too many to unnecessary surgery, which to be of value is rather mutilating and usually leaves the patient with a permanent ileostomy. One might argue that if ileostomy were performed early in all cases, frequently the condition would prove to be partially reversible, or at least not intractable, and normal bowel continuity could be re-established. We have no data to support this contention, and those few who appear to be establishing ileostomies rather early and in increasing numbers are not reporting that later closure of the ileostomy has proven feasible in any greater percentage of cases. Again, if ileostomy is performed early and later closure is successfully accomplished, it could be suspected that the case in question might have responded satisfactorily to medical management without the added risk and temporary disadvantage of an ileostomy.

The degree and stage of intractability is a relative clinical evaluation and it is difficult to state the exact criteria for surgical interference. Certainly surgery must be considered in the following conditions:

- 1) Acute, rapidly progressive, fulminating type.
- 2) Impending perforation — acute or chronic form.
- 3) Chronic intractable ulcerative colitis resisting all forms of medical therapy and incapacitating the patient for long periods of time.
- 4) Complications — perirectal abscess, fistula, stricture with obstruction, polyposis with malignant degeneration.
- 5) Severe and/or repeated bowel hemorrhage not responding to transfusions and vitamin K — questionable.

SURGICAL PROCEDURES

Appendicostomy and cecostomy are mentioned only to be condemned. Celostomy of the transverse colon is justified in the infrequent segmental ulcerative colitis involving the left colon. Ileosigmoidostomy is rarely justified as it is most unusual to find ulcerative colitis only involving the proximal colon and leaving the

rectum and sigmoid free from invasion. In only one of my own cases did ileosigmoidostomy seem indicated and to date, at the two year period, the result appears quite satisfactory. The writer has seen two patients who were subjected to primary ileosigmoidostomy by other surgeons when the rectum was apparently free of the disease, who developed a severe ulcerative proctitis within a few months.

Ileostomy is the procedure usually indicated when surgery becomes the choice of treatment. The type and position of the ileostomy stoma are important. The loop ileostomy should be used only in those extreme emergencies where it is presumed that the patient would be able to stand only the simplest and quickest of procedures. With the loop ileostomy, proximal bowel contents may spill over into the distal stoma and thus defeat the intent of placing the colon at complete rest. Also this type of ileostomy is more difficult for the patient to manage, it being especially difficult to fit a suitable ileostomy bag (Koenig-Rutzen). Later, when colectomy is done, it is technically more difficult to free the terminal ileum. The end type ileostomy is preferable. Some controversy exists as to management of the distal ileal stump in this procedure. Some favor closing the distal stump and dropping it back into the abdominal cavity. With this method, however, there exists the danger of a blow-out. Cave (5), Cattell (4), Garlock (9) and Rankin (12) now favor bringing the distal ileum onto the abdominal wall, thereby avoiding the possibility of a blow-out. It is now my preference to make an end type ileostomy and bring the distal end onto the abdominal wall. Ileostomy has been accomplished by several different techniques. I have alternated between opening the abdomen through a generous McBurney incision and through a lower left paramedian incision. In the former, after dividing the ileum, a buttonhole excision is made in the area just below and to the right of the umbilicus, the proximal ileum is brought onto the abdominal wall, the distal ileum is closed and dropped back into the abdomen and the McBurney incision closed. At the present time, I favor a technique previously used. Under combination anesthesia — local infiltration and cyclopropane with or without a little curare — a left rectus incision is made just below the level of the umbilicus. All precautions are taken not to see or touch any part of the colon. The distal ileum is usually quite easily identified as it arises from the pelvis over toward the right side, and by the ileocecal fold which is a thin fold of peritoneum usually infiltrated with fat and extending from anti-mesenteric border of the ileum to the cecum. This fold is well depicted in Deaver's (8) test book on surgical anatomy. After dividing the mesentery about 10 cm. from the ileocecal junction, the ileum is doubly clamped and divided. The proximal end is closed over the clamp with an inverting continuous catgut suture. A small buttonhole is made about 5 to 6 cm. below the umbilicus and 2 to 3 cm. to the right of the midline. The closed proximal end is delivered through the buttonhole incision, the mesentery is secured to the peritoneum of the abdominal wall and the bowel

wall to the fascia in the small buttonhole incision. These sutures prevent retraction or later prolapse. The left rectus incision is closed around the distal end and the clamp is left in place for some five or six days. The closed proximal end is then opened and a mushroom catheter placed in it to prevent abdominal wall contamination while the abdominal incision is sealing off and healing. Subtotal colectomy is carried out through a long left paramedian incision about four to six months later. The remaining sigmoid, rectum and anus are removed at the third stage some four to twelve months later. I have not attempted later anastomosis of the ileum to a rectal segment. I have been consulted in two instances where this procedure has been carried out, and in both I recommended a return to the ileostomy status. In one case, it became necessary to re-establish the ileostomy within four months and in the other within nine months.

In a recent check of 71 consecutive cases of ulcerative colitis seen over a ten year period on both charity and private services, only nine patients were subjected to surgery, a surgical incidence of twelve per cent. Eight of these were given ileostomies. Two emergency ileostomies were performed, and one patient died, which is a mortality rate of fifty per cent for emergency ileostomy. The six patients with elective ileostomies recovered, i.e., no mortality for this small series. This gives a general mortality of twelve per cent for ileostomy. The ninth patient recovered following an ileosigmoidostomy, a general mortality of eleven per cent for cases of ulcerative colitis subjected to surgical procedures. In this series, only two of those patients not subjected to surgery died. The others were dismissed as improved but we have no follow-up data at present as to whether these patients died later or had surgery elsewhere. All cases have been or are being concluded with sub-total or total colectomy. No attempt has been made to re-establish bowel continuity by simple closure of the ileostomy. Probably the failure to accomplish closure of a single ileostomy can be attributed to the policy of only offering surgery in cases where failure of medical treatment has been beyond doubt. However, by practicing this policy, the total number of ileostomies for the 71 patients is minimal. In the 63 patients not operated upon, there were only two hospital deaths, a mortality of 1.5 per cent. One of these had a progressive, fulminating ulcerative colitis, in which ileostomy carries a 50 to 75 per cent mortality, and the other was a chronic case with frequent relapses who had refused surgery a number of times.

SUMMARY

From this small series of cases, all of which could be considered moderately severe to severe in type, only twelve per cent were subjected to surgery. Possibly a more radical attitude might be taken and ileostomy performed more frequently. True, one might occasionally save another life with the policy of more frequent and earlier surgery but this policy would also give more patients ileostomies, which in itself carries a mortality rate. Also important is the fact that the

greater percentage of them probably would have been able to carry on their activities without this undesirable procedure. At present, we do not have sufficient evidence to conclude that early ileostomy in ulcerative colitis will result in permanent cure of the disease and permit permanent closure of the ileostomy and re-establishment of bowel continuity, thus avoiding permanent ileostomy. It is my impression that the

case ileostomized in the early stage without an adequate trial by medical management, with subsequent successful closure of the ileostomy, is the type which would have responded satisfactorily to proper medical management. However, ileostomy at times is definitely life saving and at other times is the only means by which we can make ulcerative colitis compatible with life.

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Comments on the Laboratory Diagnosis of Enteric Infections

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THE RAPID PROGRESS in bacteriology, parasitology and serology during the last years constantly increases the difficulties faced by the gastroenterologist and his laboratory aid when methods of examination have to be selected which can be carried out in a small laboratory without the use of elaborate apparatus, large series of diagnostic sera and much special experience. While the authors discussed laboratory procedures suitable for large, well-equipped establishments with highly specialized personnel at great length in other papers (1, 2), this article is destined for the use of small laboratories adjacent to the office of the gastroenterologist. The methods described here are, therefore, not necessarily identical with those recommended for large establishments. The efficacy of the procedures described in the present paper is somewhat lesser than that achieved by more intricate and more extensive methods. The statistical analysis of these procedures, however, shows that their probability of success is higher than .90. Even better results can be achieved by repeated examinations. Thus, in the long run, the final outcome of the series of examinations using simple methods will be the same as if more extensive procedures are applied to a fewer number of specimens.

In the experience of the writers, which is probably shared by most laboratory workers, the crucial

points of the examination lie not only in the selection of the proper method but, even to a larger extent, in the way the method is put into practice. The cardinal requirements may be summarized as:

- 1) Proper method of specimen collection.
- 2) Immediate preservation or examination, avoidance of drying.
- 3) Selection of the most suitable portion of the specimen.
- 4) Properly prepared media, stains and reagents.
- 5) Satisfactory technic of inoculation and fishing colonies.
- 6) Correlation of biochemical and serological reactions.

If these points are kept in mind, the methods here described will not fail to give satisfactory results. They will be discussed in detail in the subsequent chapters describing the techniques.

For the diagnosis of so-called "enteric" infections, stools, urine and blood are usually examined. Urine examination is important in Salmonella infections, because these organisms are often excreted through the kidneys, chiefly in typhoid and typhoid-like fevers.

STOOL EXAMINATION

For routine examination, we disregard anaerobic organisms, yeasts and molds, because of the difficulties encountered in their identification. The significance of these organisms in the intestine has not been established as yet.

If Streptococci are the object of our search, as they may be in ulcerative colitis, one or two blood agar plates may have to be added to the series of bacteriological media. The differentiation of Streptococci isolated from the intestinal tract should not be attempted in a small laboratory because of the great number of biochemical and serological tests required in this work.

In America, the chief interest of laboratory workers is directed toward Shigellae (dysentery bacilli), Salmonellae (typhoid-paratyphoid-enteric bacilli) and parasites. No stool examination is complete without a search for these bacteria, protozoa and helminths. One of the greatest mistakes made in stool examination, chiefly in chronic intestinal disturbances, is to test the stool either only for bacteria, or only for protozoa. The features of amebiasis (types II and III of Craig) resemble so closely forms of bacillary infections that differential diagnosis is impossible without the aid of the laboratory.

The stool has to be fresh and examined not later than fifteen minutes after collection. If such examination is impossible, preservatives have to be used.

Stool collection. The ideal method to collect stools is the procedure described by D'Antoni (3). This method can be carried out only by a gastroenterologist. The patient receives a saline cathartic. A cleansing enema is given. Pre- and post-cathartic stools are collected. The fecal material evacuated after the saline enema is also sent to the laboratory. Finally, sigmoidoscopy is performed. Material is collected with the aid of a suction bulb and with proctologic swabs.

It is not possible to collect material in this way in all cases. We have to be satisfied with diarrheic stools and rectal swabs (preferably collected according to the well-known procedure of Hardy and Watt) in cases of diarrhea. When the lesions sit in the higher parts of the intestine and no diarrhea is present, as, e.g., in shigellosis or amebiasis involving predominantly the ascending colon, post-cathartic stools are more informative. It should be a general rule to examine both post-cathartic and sigmoidoscopic specimens.

A stool specimen evacuated in a toilet near to the laboratory can reach the table of the bacteriologist easily within a few minutes. Sigmoidoscopic swabs, however, will dry out before they are brought to the laboratory. It is recommended, therefore, that one or more such swabs are dumped into peptone broth (for bacteriologic examination) and others used by the gastroenterologist for the preparation of permanent slides (for protozoa). The gastroenterologist is furnished with a Coplin jar filled with Schaudinn's fixative and a few slides. He streaks the fecal material to the slides and places the slides immediately in the fixative. The Coplin jar is brought to the laboratory at a convenient time, together with the peptone broth tubes into which the swabs destined for bacteriologic examination were put.

Stool preservation. If stools cannot be examined immediately, they have to be preserved. Two collecting bottles, one ounce each, are used. One of the

bottles contains about 20 cc. of 10% formalin, the other about 20 cc. of the fluid of Bangxang and Eliot (see Appendix No. 1). About one gram of the fecal material is thoroughly mixed into each of the bottles. Formol will preserve parasites indefinitely, while Bangxang's fluid will keep Shigellae and Salmonellae alive for about one week.

Stool examination. If possible, a mucous part of the stool is used for examination. Two alternative methods may be used for the bacteriologic testing of stools, both employing plating media which are easy to prepare. It is essential that the plates are sufficiently thick (about 1/4"). Their surface shall be dry. Plates older than four days shall not be used.

Either two S. S. Agar plates (Difco) or two to three E. M. B. (Eosine methylene Blue, Difco) plates are streaked. It is important that a good streak, giving many isolated colonies, e.g., the clock-streak, is used. After 24 hours' incubation, colorless, yellow or brownish colonies are picked to T. S. I. medium (B. B. L.). When S. S. plates are employed, one tube of Tetrathionate broth (Difco) is also inoculated.

The tube is incubated for 24 hours, then streaked to a Bismuth Sulfite Agar plate (Difco) which is incubated for 48 hours. Black colonies with a halo and metallic sheen are picked from this plate to the T. S. I. medium. Instead of the tetrathionate broth, two brilliant green E. M. B. plates (11) may be streaked. They are picked after 24 and 48 hours incubation.

The growth from the T. S. I. medium is studied according to the reaction observed after 30 to 32 hours incubation.

If there is an alkaline slant, an acid butt and no gas formation, Shigellae and typhoid bacilli are suspected. The growth is inoculated into:

One tube of semisolid mannitol (see Appendix No. 2).

One tube of peptone (preferably tryptone or medo-peptone) broth.

One or two agar slants.

The next day motility in the semisolid mannitol is observed. Shigellae are non-motile, while typhoid bacilli are motile. Thus Shigellae will have grown only along the line of stabbing, while typhoid bacilli will spread out into the medium. Typhoid bacilli ferment mannitol, while Shigellae may be mannitol-positive or negative.

The growth in peptone broth is used for the indole test. Typhoid bacilli do not produce indole; neither do Sh. dysenteriae, Sh. sonnei and a number of the Sh. paradysenteriae Flexner-Boyd strains.

The growth from the surface of one agar slant is used for agglutination tests. The slide agglutination method is recommended for small laboratories, using commercial (Lederle) sera. The technic described in the pamphlets enclosed with these sera have to be followed in minute detail. There is no use in testing the suspected strains with other sera than those indicated by the biochemical reactions of the organism. E.g., indole positive Shigellae shall not be tried with Sh. sonnei serum.

TABLE I
Biochemical Properties of Shigellae and Salmonellae

T.S.I. Medium			Semisolid Mannitol		Indole	Rhamnose	Dulcitol	Organism
Slant	Butt	H-2 S	Motility	Fermentation				
k	A	O, exceptionally little	O	O	O	O	O	<i>Shigella dysenteriae</i>
			O	A	+	+	O	<i>Shigella ambigua</i>
					mostly +	O	O	<i>Shigella paradysenteriae</i>
					+	rare late A		Flexner-Boyd
k	A	O	O	A	+	+	+	<i>Shigella alkalescens</i>
slow A					O	+	O	<i>Shigella sonnei</i>
k	A	slow	+	A	+	+	varies	<i>Shigella disoar</i>
k	G	varies	+	G	O	X	X	<i>Salmonella typhosa</i>
					O	X	X	<i>Salmonella</i>

Explanation:

k — alkaline A — acid G — acid and gas
X — test not necessary but organism has to be Voges-Proskauer negative.

Typhoid bacilli usually form some hydrogen sulfide, which reveals itself by a small amount of blackening in the T. S. I. tube. This blackening may develop late. Rarely strains of *Shigella* also give this reaction.

Misleading reactions occur chiefly when dried T. S. I. tubes are used. Such media do not show gas formation when inoculated with organisms producing gas and thus may support false suspicion of *Shigellae*.

So-called anergenic paracolon organisms which give reactions similar to those of *S. typhosa* or *Sh. dispar*, are rare. They are usually motile and form indole.

The diagnosis of *Shigella* strains has to be confirmed by further biochemical tests. Tubes containing rhamnose and dulcitol (see Appendix No. 3) are inoculated. Table I shows the results of such reactions.

If the organism produces in T. S. I. medium an alkaline slant, acid and gas in butt, *Salmonella* (other than typhoid bacillus) is suspected. Most *Salmonellae* isolated in the United States form hydrogen sulfide, causing blackening of the medium. Protei and paracolon organisms produce similar reactions. Many of them may be excluded by discarding T. S. I. tubes emitting a strong, unpleasant odor. *Salmonella* ferment mannitol and do not produce indole. They are also Voges-Proskauer negative.

The following media are, therefore, inoculated:

One tube of semisolid mannitol (see Appendix No. 2).

One tube of peptone (preferably tryptone or medo-peptone) broth.

One tube of V. P.-M. R. medium (Difco or B. B. L.).

After 24 hours, all cultures which do not show fermentation of mannitol or which produce indole are discarded. From the V. P.-M. R. tubes of the remaining cultures two agar slants are inoculated.

One day later, the T. S. I. medium is re-checked, if the slant is still alkaline. If not, the culture is discarded. The Voges-Proskauer reaction is performed, using Leifson's technic (see Appendix No. 4). If

the reaction is negative, the growth on the agar slant is tested with *Salmonella* sera (Lederle).

It is a desirable procedure to mail cultures which cannot be identified to a *Salmonella*-*Shigella* typing center. Such centers will gladly check diagnoses of strains made in small laboratories.

Most doubtful results are the outcome of working with impure cultures. Improper streaking resulting in few isolated colonies, careless fishing of the colonies during which neighboring colonies are touched and other technical mistakes may introduce a mixture of organisms into the T. S. I. tube. The media recommended for the plating of stools are highly inhibitory for many non-pathogens, nevertheless such organisms remain alive on them. Thus, when colonies are picked, only the center of the colony shall be touched with the needle.

The described method is somewhat lengthy. It gives, however, good results and permits saving media, sera and manpower.

For the detection of parasites, the methods differ according to the goal of the examination. Helminths and their eggs may be found in direct smears and with flotation methods. A biopsy of the rectum may be necessary in schistosomiasis. Helminthic examination, except in direct smears, do not fall within the scope of this paper. A search for protozoa is always indicated. The chief aim is to discover *Endamoeba histolytica*. Other protozoa, however, also may play a role in intestinal disorders (4).

When searching for protozoa, the most important point is to examine the material as soon as possible (within 15 minutes after the specimen was collected when no preservative is used), and that the slides never are allowed to dry during the procedure. Many laboratory workers are afraid to dump wet smears into the fixative or wait for the evaporation of the xylol before covering the slides. Such hesitation results in worthless preparations.

Saline, iodine tinged smears and permanent slides are recommended for the diagnosis of protozoa.

The saline and the iodine smears are prepared on the same slide. One drop of saline and one drop of D'Antoni's iodine are put on two different ends of the slide. One drop of fecal material is mixed into each of them and cover slips are applied.

The permanent slides are prepared by smearing the fecal material on the end of at least two, distinctly marked (with name and number) slides and placing the slides in Schaudinn's fixative (see Appendix No. 5). If the material is very liquid, some egg-albumin may be used to increase its adherence to the slides. It is recommended that the fluid is kept in Coplin jars. When the slides are prepared in pairs and put into the fixative back-to-back, material from as many as five stools may be fixed in one jar. Slides are prepared from fresh specimens as they arrive at the laboratory during the day. The jars are left standing until the next morning. The slides, however, may remain in the fixative for as long as 48 hours. After fixation the slides are run through the following series:

- 5 to 10 minutes in 95 per cent alcohol containing enough iodine tincture to give it a port-wine color.
- 5 to 10 minutes in 95 per cent alcohol.
- 5 to 10 minutes in 70 per cent alcohol.
- 5 to 10 minutes in distilled water.

Mallory's hematoxylin (see Appendix No. 6), according to the strength of the stain, from a few hours to 48 hours.

There is, usually, a great width of permissible variation. Most solutions give a good stain in 4 to 24 hours. Thus the slides reach the hematoxylin in the morning, they are removed from it in the evening or the next morning.

5 to 10 minutes differentiation in tap water, until the slides turn dark blue, but not longer than 10 minutes.

- 5 to 10 minutes in each of the following:
 - 70 per cent alcohol.
 - 95 per cent alcohol.
 - Absolute alcohol.
 - Xylol.

Mount in Clarite or Canada balsam.

Such slides may be examined at leisure. More material can be seen than when only saline smears are examined. A more detailed study of the protozoa is possible. Much information regarding other cellular elements in the feces can be gained. Finally, the slides may be kept as permanent records for about one year.

This modification of Ratcliffe's and Parkins' stain (5) has been used by us for several years, with excellent results. It is not superior to the flotation technique but it is easier to apply in a small and busy laboratory. It gives better results than the presently used culture methods for amebas.

URINE

Urine is collected into Tetrathionate broth (Difco) and incubated for 24 hours. After this, one S. S. and one Bismuth Sulfite plate (Difco) are streaked from the broth and the growth treated as in work with stools.

BLOOD

Blood Culture. Blood cultures are positive during the generalized (septicemic) phase of numerous Salmonella infections. Antibiotics and sulfa drugs, even if not resulting in cure, distort the classic picture of salmonellosis to such an extent that the clinical diagnosis is nowadays difficult in localities where such drugs are routinely administered to febrile cases. Requests for blood cultures for Salmonellae are becoming rare, thanks also to the increasing standards of municipal sanitation which make typhoid fever a rare occurrence. The question has to be answered as to whether routine blood culture media, designed primarily for the isolation of Streptococci, Brucellae a.o. from the blood, are satisfactory for the isolation of Salmonellae or if a special medium, as bile-broth, Selenite-F or Tetrathionate broth should be used routinely together with other blood culture media.

A series of experiments was set up, employing bile-broth, Selenite-F (B. B. L.), Tetrathionate Broth (Difco), Brain Broth Infusion with P. A. B. (Difco), Thioglycollate Fluid Medium (B. B. L.), Tryptose broth, Trypticase Soy Broth (B. B. L.) and Kracke's Medium (Difco). Series of five tubes, each containing 20 cc. of the respective medium, were used for each experiment. To each tube 2 cc. of human blood containing less than ten anti-Salmonella mouse protecting units per cc. were added. Groups of five such tubes each were inoculated with 20 2 organisms as S. paratyphi A, S. typhi-murium (two strains), S. paratyphi B, S. paratyphi C, S. cholerae-suis (two strains), S. newport, S. oranienburg, S. typhosa (three strains) and S. panama, respectively. Plate counts were performed (in quintuplicates) after 24 and 48 hours. It was found that, with the exception of the thioglycollate medium (which does not enhance the growth of Enterobacteriaceae) all media gave higher bacterial counts than bile-broth, Selenite-F and Tetrathionate broth. Thus, routine media employed for hemoculture are satisfactory also for the detection of Salmonella bacteremia.

TABLE II
Multiplication of Salmonellae in Routine Blood Culture Media

Medium	Mean multiplication factor in 24 and 48 hours for Salmonella									
	para A	para B	para C	typhosa	typhimurium	cholera-suis	newport	oranienburg	panama	
Bile-broth	11	17	10	15	23	16	19	22	23	
Selenite F	15	20	17	19	25	20	24	29	26	
Tetrathionate	12	19	16	17	25	25	25	27	25	
Brain-broth	24	27	29	21	28	25	28	27	29	
Tryptose broth	25	25	26	27	30	28	28	30	28	
Trypticase Soy broth	26	30	32	28	32	33	31	33	31	
Kracke	20	22	20	22	28	25	27	26	25	
Thioglycollate	.02	.05	.01	.07	.09	.03	.02	.02	.02	

Multiplication factors are given in hundred thousands.
Serodiagnosis. The serologic diagnosis of "enteric" infections from the blood of the patient is a crucial

method. As Weil pointed it out recently (6), agglutination experiments for the detection of *Shigella* antibodies in the sera of the patients are difficult to interpret. According to our personal experience, such tests are of little or no value and should be abandoned until better laboratory methods are devised for the detection of blood agglutinins in shigellosis.

Agglutinating antibodies in salmonellosis can be evaluated only if the patient has not been immunized against typhoid fever and did not suffer from salmonellosis previously. There is much cross-reaction between *Salmonellae*. One has to keep in mind that the type diagnosis of *Salmonellae* is established with the aid of rabbit sera, manufactured by injecting such organisms into the vein, while in sick patients we deal with human sera in which antibodies were formed chiefly following the activities of the causative organisms in the intestines. It is suggested (7), therefore, that polyvalent antigens are used and that only rising agglutinating titers are considered diagnostic. Due to cross-reactions and minor antigens, it is impossible, in most instances, to establish the diagnosis

of the causative organism from the outcome of the agglutination tests with the patient's serum.

The Vi agglutination test is not a procedure applicable in a small laboratory.

Complement fixation tests are useful in amebiasis. Rees et al. (8), Boe (9) and Kent and Rein (10) contributed much to the production of a reliable laboratory method. The antigen is available commercially. According to our experience, the reaction is always positive in amebic liver abscess and diffuse hepatitis. The number of positive cases is lower in patients having only slight intestinal lesions or without clinical symptoms. Our restricted material, however, does not permit a final judgment.

SUMMARY

Laboratory methods routinely used for the diagnosis of shigellosis, salmonellosis and amebiasis are discussed. Simple procedures are described which may be used in small laboratories. Some pitfalls in the laboratory technic are emphasized.

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APPENDIX

(1) Preserving Fluid of Bangxang and Eliot, modified.

Dissolve Sodium chloride 5 Gm.
Sodium desoxycholate 5 Gm.
Sodium citrate 10 Gm.
Peptone 5 Gm.
in Distilled water 1 L.
Adjust pH to 7.6 to 7.8.
Add 3 cc. of a 1% solution of Disodium phosphate.
Fill about 20 cc. in 1 oz. screw-capped bottles.
Sterilize in flowing steam for 20 minutes.

(2) Semisolid Mannitol.

Dissolve Agar 3 Gm.
Sodium chloride 5 Gm.
Proteose-Peptone No. 3 or Trypticase 10 Gm.
Mannitol Difco 10 Gm.
in Distilled water 1 L. by boiling.
Adjust pH to 7.4 to 7.6.
Add 4 cc. of a 0.4% watery solution of Brom cresol purple.
Fill into test tubes.
Autoclave for 25 minutes at 15 lb. pressure.

(3) Rhamnose and Dulcitol.

Dissolve Sodium chloride 5 Gm.

Proteose-Peptone No. 3 or Trypticase 10 Gm.
Rhamnose or Dulcitol 5 Gm.

in Distilled water 1 L.

Sterilize by filtration or tube into screw-capped tubes and autoclave for 15 to 20 minutes at 10 to 12 lb. pressure. Check for sterility by incubating for 48 hours.

(4) Voges-Proskauer Reaction.

Reagent of Leifson:

Dissolve 1 Gm. of Copper sulfate in 10 cc. distilled water.

Add 40 cc. concentrated ammonia.

Add 950 cc. of a 10% solution of Sodium hydroxide.

Reaction:

After 48 hours (or longer) cultivation in V. P.-M. R. medium, add to the growth an equal volume of the reagent. Observe result (copper discolorization) after 30 minutes.

(5) Schaudinn's Fixative, modified.

Saturated solution of Mercury bichloride in dis-

filled water 200. cc.
96% alcohol 100 cc.
The day of use add to each 100 cc. of this mixture 7 cc. glacial acetic acid.
Make up new solution at least every third day.

(6) Mallory's Hematoxylin.

Dissolve 0.1 Gm. hematoxylin in 50 cc. boiling

distilled water.
Dissolve 2 Gm. phosphotungstic acid in 20 cc. distilled water.
After cooling, mix both solutions and make up with distilled water to 100 cc.
Let ripen for 6 to 8 weeks or add 10 cc. of a freshly prepared 0.25 per cent solution of Potassium permanganate.

Appetite and Overeating in Their Relation to Obesity *

By

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HYPERPHAGIA, that is, excessive food intake, is offered as explanation of various types of obesity both in man and experimental animals. Faulty habits and psychic factors (1) should account for human hyperphagia. Psychic factors, particularly, seem to appeal to the fashionable psychosomatic trend in modern medicine and a host of publications on this subject appeared in the last few years not only in the medical but even in the lay press. Obesity became a "behavior problem" rather than a metabolic disorder. In 1945 I did not hesitate to consider such a shift as absurd (24). With animals made obese by experimental hypothalamic lesions it is not quite as simple. Rightfully Brobeck (2) raises the question: "Why does the animal with hypothalamic lesions eat so much extra food? . . . What changes in the internal environment set the animal to eating, and what changes are associated with satiety?"

As nobody is in doubt that the law of conservation of energy holds also for the animal body, and as it is an established fact that any surplus of intake of energy as compared with its output leads to accumulation of fat in the body, obesity may be called the result of an imbalance between energy intake and energy output. Such a statement, however, is a tautology rather than an explanation of the nature of obesity. Many authorities have emphasized the fact that normal persons must be protected against such an imbalance in some way; otherwise the majority would become obese. As a matter of fact, they are well protected. The automatic regulation of intake and output of energy is controlled rather precisely by a number of so-called general feelings, such as appetite, hunger, satiety and the desire for muscular activity or for its restriction, the latter being due to fatigue, weakness or exhaustion. But it is not only this nervous regulatory mechanism which tends to maintain the body weight. The thyroid, as well, adapts its activity to the requirement. It restricts the production of hormone and herewith the oxidative processes in the body if an insufficient amount of food intake

threatens the maintenance of the balance, and it functions in excess if overfeeding is going to increase unduly the body weight. This adaptive power characterizes the living organism as compared with a physicochemical machine. If exogenous, or simple, obesity is defined as the result of maladjustment between food and exercise, then it requires a breakdown of the mentioned regulatory mechanism, which is represented by endogenous functions of the living body. In other words, an exogenous obesity is always an endogenous one also.

The desire to eat and drink is a general feeling serving the organism to build up the necessary quantity of body tissue, to supply the energy for vital functions, and to maintain the body weight at an approximately equal level. It is the requirement of the organism, both quantitative and qualitative, which rules the appetite under normal conditions. Appetite for sodium chloride or for calcium, for instance, is influenced by the functional condition of the adrenal or the parathyroid glands, respectively, as Richter and Eckert (3) demonstrated in interesting animal experiments. Putnam, Benedict and Teel (4) produced typical acromegaly and gigantism in a young female dog by treating it for fourteen months with intraperitoneal injections of an extract of the anterior lobe of the beef pituitary containing the growth-promoting principle. The dog acquired a ravenous appetite, but no one is likely to assume that daily intraperitoneal injections of pituitary extract stimulated it primarily. Everyone will rather assume that the injections provoked a tendency toward increased proliferation of cells, leading to gigantism and acromegaly, and that this increased cellular activity required a greater amount of energy, and in turn led to an unusual intake of food. The increased appetite is, therefore, to be looked upon as an interposed factor, not directly influenced by the injections but indispensable for the realism of gigantism and acromegaly which the growth-promoting substance finally produced.

A similar situation has been encountered in rats treated with thyroxin (5). They eat almost double but nevertheless lose in weight. Thyroxin certainly does not increase the appetite directly but by the

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adaptation of the body to the increased requirement of food in order to maintain the body weight.

The existence of primarily ill-trained or hereditarily abnormal appetite causing obesity has been assumed.

I am very much in doubt, however, whether it is possible to produce obesity artificially in a normal person. What may be produced by artificial over-feeding or artificial restriction of muscular activity is a temporary overweight, corpulence or fatness, but not persisting obesity. The German language seems to be the only one which differentiates between "Fettleibigkeit," that is, the state of fatness, and "Fettsucht," that is, the tendency to become fat.

Many facts speak in favor of the concept that hyperphagia might be the consequence of the primary tendency to overweight; that it is a necessary means for the realization of obesity (6). The primary tendency to overweight can have different causes. The following classification fits the facts, in my opinion, most adequately from both theoretical and practical viewpoints.

I. Symptomatic obesity.

1. Endocrine (hypothyroid, hypogonadal, adrenal cortical, pituitary, insular pancreatic).

2. Cerebral (hypothalamic).

II. Constitutional obesity.

1. Symptomatic obesity. — It is not within the scope of this paper to elaborate on the various forms of symptomatic obesity. They are infrequent as compared with the constitutional variety. Among 275 unselected cases of high grade obesity, there were only five cases of endocrine and two cases of cerebral adiposity (7). In all of the remaining 268 cases no such diagnosis could be made. If some symptoms or signs suggestive of an endocrine disturbance were found, they were evidence not that an endocrine disease was causing the obesity, but merely of what we call "endocrine stigmatization" (8). This term is used for structural or functional deviations that ought to be considered as indicators and side effects of an abnormal constitutional (genetic) setup rather than as the underlying cause of a particular constitutional disorder. Such signs of endocrine stigmatization may be irregularity of the rhythm or intensity of menstruation, a late or premature onset or cessation of the menses, sterility, ovarian cysts, abnormality of hair distribution, diffuse or nodular enlargement of the normally functioning thyroid, and others.

The etiology of symptomatic obesity is a disease of the respective endocrine glands or of the hypothalamic region of the brain. Obesity is one of its symptoms. The pathogenesis of this obesity is only partially explained by changes of heat production, overeating and restriction of muscular activities. There is evidence that alterations of the intermediary metabolism play an important role. Animals with hypothalamic obesity have been shown to transform dietary carbohydrates into fat at a tremendously accelerated rate (9). This occurs through the mediation of insulin, which promotes the accumulation of ingested carbohydrates and its transformation first into glycogen and then into fat in the adipose tissue (10). A dramatic gain in

weight has been observed within a few hours after hypothalamic lesions. At this time the animals exhibit considerably increased muscular activity and "run almost continually in an automatic almost frenzied fashion for several hours after they awake from the anesthetic" (Hetherington and Ranson, 11). Reduction of energy expenditure is, therefore, not a factor in the production of this type of obesity.

To decide whether hyperphagia or alteration of the intermediary metabolism is the primary disturbance experiments with restricted constant food intake are paramount. They revealed that even under these conditions hypothalamic lesions induce overweight in animals which do not eat more than the controls. Accordingly, "a disturbance in fat metabolism of a nature that actually enhances the laying down of fat in the various fat depots" (Keller et al., 12) must be the primary effect of the hypothalamic lesion, and hyperphagia its secondary, indirect consequence or, at best, a parallel phenomenon. A similar situation is encountered in young normal rats when treated with growth-promoting hormone from the anterior pituitary gland. These rats gain significantly more weight than do untreated litter mates, although food intakes are being kept identical for experimental and control animals. This fact, observed by Lee and Schaffer (13) and by the H. M. Evans group (14) of investigators, led to the conclusion that the growth-promoting action of the hormone cannot be ascribed to increased food intake. The resulting deposit of tissue substance must, therefore, be considered a consequence of better utilization of the food eaten.

Another fact proves that hyperphagia alone is not sufficient to explain the phenomenon of obesity: The unequal distribution of fat accumulation in the adipose tissue of the body. Different parts of the adipose tissue exhibit a different tendency for such an accumulation, they have a different "lipophilia." A local factor must, therefore, be involved. That the fat distribution in male castrates, eunuchoids and those whose endocrine testicular function has been abolished by a pituitary or hypothalamic disease, shows the characteristic female (or eunuchoid or asexual) type can only be explained by the assumption that the testicular hormone inhibits the lipophilia at certain parts of the body surface such as the breasts, the lower abdomen, the hips and thighs (15). Hence also this same fat distribution in obese boys whose testicular hormone is not yet available in sufficient quantity to check the lipophilia in the particular regions. All fat boys exhibit this eunuchoid or better asexual fat distribution (15, 16, 17). The fact that this phenomenon was not understood led to the erroneous conclusion that such boys suffer from hypogonadism or from Froehlich's dystrophia adiposo-genitalis. It took more than 20 years until the correct interpretation had been generally accepted.

The characteristic fat distribution about the face, neck and shoulders encountered in adrenal cortical tumors and in Cushing's disease proves that the adrenal cortex, too, exerts an influence upon the lipophilia of the adipose tissue. To deny the existence of endocrine

obesity quite generally would be spilling the bath with the baby.

II. *Constitutional obesity*. — In the large majority of cases obesity is not a symptom of an endocrine or hypothalamic disease. To consider hyperphagia for psychic or other reasons as its etiologic factor is overlooking certain fundamental facts. *Heredity* as an etiologic factor of most cases of obesity can hardly be questioned anymore. Danforth's (18) strain of mice presenting extreme obesity linked with a yellow color as a hereditary, dominant mendelian characteristic has its analogon in human pathology. Statistical studies, investigations on identical twins, and simple observation in daily practice of obese patients and their families are proof of it. It must be an abnormal gene or gene-complex, not faulty habits of eating, that accounts for this truly constitutional type of obesity. Not all members of a family living in the same environment, but only those who inherited the abnormal gene, become stout. The stocky body build of these persons is an almost invariable attribute of this gene or gene-complex. It is difficult to understand how the hereditary character of this body build can be admitted and that of obesity be denied (19).

It has been assumed that the abnormal gene might cause a hereditary abnormality of appetite and consequently hyperphagia (20). This is invalidated by the fact that the gene may act before appetite as a general feeling exists. It fits into the general panel of the physiology of genes that the time of actual manifestation of their potentialities may vary in different strains. As far as the genes accounting for obesity are concerned, their manifestation in exceptional cases may take place soon after birth or even in fetal life. These are the cases described by T. Christiansen as "macrosomia adiposa congenita" (21). In the family reported by this author, two sisters had five children each. Three and four respectively of the two sets of children were rather large at birth. These babies immediately after birth displayed extraordinary appetites, grew very rapidly, and accumulated prodigious amounts of fat. Only one of them survived the first year. Autopsy performed in one case did not reveal any explanation of the peculiar condition. From this observation the inference must likewise be drawn that overfeeding must be considered the compulsory consequence rather than the cause of obesity. Overfeeding is nothing but the indispensable means to the realization of the potentialities of the abnormal anlage.

Pool (22) reported a case of macrosomia adiposa congenita who had been studied by us in some detail. An extreme familial obesity in a twelve year old girl was associated with polydactyly, syndactyly, hypophalangism due to an abnormal fusion of the phalanges, a marked congenital deformation of the skull classified as acrocephaly, and intellectual deficiency. At birth the girl had a weight of 6 kg. (13.2 pounds). This fits into the picture of Christiansen's "macrosomia adiposa congenita." At the age of twelve years the weight was 182 kg. (400 pounds), the height 157 cm. Two brothers of the mother had a body weight

of 160 kg. (352 pounds) each, a third weighed 110 kg. (242 pounds).

In cases of this sort it cannot be an abnormal appetite that causes obesity unless we use this word in a different than the usual sense: *Appetite, not as the general feeling, as a psychologic category, but appetite of a bodily tissue, that is, as a biologic category*. If we shift to this phylogenetically more primitive concept of the term "appetite," then it is true, the gene responsible for obesity does cause abnormal appetite of the fat tissue. This, in turn, results in excessive appetite in the usual sense of the word and causes hyperphagia without which its actual manifestation would be impossible.

For animal breeders the hereditary etiology of obesity is an established fact. They know that hereditary obesity is the result of more efficient food utilization (25). There are strains of rats that gain more rapidly in weight and require about thirty per cent less food per gram of gain in weight than other strains. The "yellow" gene of Danforth's adipose mice was shown to accomplish the increased fat deposition in spite of a lowered food requirement per unit of gain as compared with normal mice strains. The appetite was only slightly increased.

If we use the word lipophilia for such an "appetite of the fat tissue" it becomes evident that it depends not only on certain endocrine factors, as we mentioned previously, but that its physiological regional differences are dependent on a hereditary factor. Anybody paying particular attention to this point can see that the various types of distribution of subcutaneous adipose tissue are hereditary traits. The so-called girdle type, the trochanteric or breeches type, the inferior type with lipomatosis of the legs, or the superior type with accumulation of fat in the neck, face, breasts, back and upper parts of the arms, are not the result of particular endocrine disturbances in women but are constitutional, that is, genetic variants. Excessive accumulation of fat at the buttocks known as steatopygia has even become a racial characteristic of certain Negro tribes. This fact alone proves its genetic origin since all racial characteristics must once in the past have been constitutional traits. It stands to reason that regional lipophilia must be subject to quantitative individual differences.

Recognition of regional lipophilia logically involves recognition of lipophilia quite generally. "Adipose tissue is not merely a storehouse; it is also a manufacturing plant in active operation, not only producing some or all of its own stored materials . . ." (H. G. Wells, 23). In any discussion of obesity adipose tissue must not be "a neglected subject." The gene or gene-complex that is the primary cause of obesity, seems to be somewhat similar to the gene responsible for the height of the individual. Nobody questions that the latter is a constitutional and, to a certain extent, a racial characteristic. This gene extends its activity upon various tissues such as the epiphyseal cartilages and the endocrine organs which regulate growth, that is particularly the anterior pituitary. Accumulating a definite amount of adipose tissue, and

thereby reaching and maintaining a definite body weight, constitutes a unitary biologic process controlled by a particular gene or gene-complex. The actual manifestation of this gene-complex, however, is spread over a large area of various organs and functions. These are the adipose tissue, the endocrine organs and the hypothalamus, which are involved in the regulation of metabolism, of energy intake and output. Lesions of these organs may cause obesity of the symptomatic variety. In constitutional, ordinary obesity their functions are integrated at a different level by the action of the abnormal gene or gene-complex, without evidence of a disease of any one of these organs.

It is not intended to discuss implications deriving from this concept of obesity. That has been done on previous occasions (24). One point only may be emphasized. We cannot extend our therapy to genes. Yet we can change the environment indispensable to the realization of the potentialities of the genes, and we may counteract their activity by interfering with the mechanism of the realization. A normal person regulates his intake and output of energy automatically because of such general feelings as appetite and

satiety and because of his glandular and nervous functions. A person with constitutional obesity which he wishes to suppress cannot rely on his automatic regulations and must follow a certain regimen which counteracts them. In other words, the obese person is forced to eat and drink not what he wants but what his physician considers useful. He cannot rely on his automatic regulations if he wishes to avoid the consequences of his constitutional trait.

Energy and willpower are necessary to overcome the desire to eat more than has been prescribed. This is the point at which psychotherapy may be requested in some cases. It does not mean, however, that obesity is primarily a mental disease. *In fact, it is a metabolic disease. It may be caused by an abnormal genetic factor which accounts for the gearing of energy equilibrium at an abnormal level. This is the most frequent ordinary type of constitutional obesity. Or it may be caused by a disease of one of those organs that are involved in this gearing of energy equilibrium. This is the symptomatic type of obesity.* Emotional factors which have been so abundantly emphasized in the recent literature at best can be cooperating factors but hardly the cause of obesity.

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Use of Non-Nutritive Materials to Satisfy Hunger

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CRUDE NON-NUTRITIVE MATERIALS, such as ground bark and wood pulp, seem to have been used throughout human history in attempts to satisfy hunger under famine conditions. Such materials were used extensively in Europe during the first World War but a great increase in gastro-intestinal disorders was attributed to their use. As a result, little use appears to have been made of such materials during the second World War. In China, kaolin seemingly was first used to still hunger under famine conditions. In the starvation treatment of diabetes before insulin was discovered, washed bran (bran with the starch washed out), vegetable pulp (thrice boiled vegetables), agar, karaya gum, talcum powder, ground corn cobs, ivory nut flour, cellulose flour, mineral oil and saccharine were used in attempts to satisfy hunger. Some of these materials are still used in the dietary management of diabetes and also obesity. However, I believe that non-nutritive substances would be used more widely to make food restriction easier if their value (and limitations) were better understood and if more satisfactory ready-to-eat products were available.

Obviously, non-nutritive substances do not satisfy like food and they can even arouse or increase the desire to eat. This was noted in 1925 when Dr. Kleitman and I made studies of basal metabolism (1) and hunger (2) in connection with my 41-day fast. I tried to prevent the development of gastric "hunger" contractions while the basal metabolism tests were made by ingesting a quantity of non-nutritive material just before the basal tests were made. Records of gastric motility were simultaneously made by the balloon method. Although I ingested enough of the non-nutritive material to produce a marked sense of fullness, strong gastric "hunger-like" contractions were usually recorded within five minutes (1). When nothing was ingested, periods of gastric "hunger" contractions developed only at two- to three-hour intervals. The non-nutritive material (a simple mixture of cellulose flour and petrolatum flavored with saccharine) obviously stimulated the gastric motility and the stomach rapidly became empty again with resulting gastric "hunger" contractions and sensations.

The reaction of the stomach to the non-nutritive material (tendency of the stomach to contract) explained why only a moderate amount could be ingested before a marked sense of fullness developed and the rapid emptying of the stomach explained why I usually found it necessary to swallow additional amounts of non-nutritive substances at short intervals to keep myself more or less continuously satisfied, especially after nothing was ingested during the pre-

ceding twelve or more hours. However, I generally found that the intervals between the periods of feeling empty or feeling "hollow hunger" became longer as a result of the successive ingestion of moderate amounts of non-nutritive materials and a sense of more or less prolonged and practically complete contentment often developed eventually. This appeared to be explained about 1932 when Dr. Paul C. Hodges made X-ray observations on me after I ingested an unusually large amount of semi-opaque material. A mixture of cellulose flour, barium sulphate and powdered karaya gum was used. This was flavored with a minimum of brown sugar as a strictly non-nutritive mixture was not needed for our purpose and brown sugar tasted better than saccharine. Enough water was added to make a dough-like product. The object was to determine whether enough of such a mixture could be consumed to outline the small intestine. I ate as much as I could of the mixture from early in the morning until about 2:00 P. M., when I felt that it would be impossible to ingest much more during the remainder of the day. I felt as if my stomach was not merely full but greatly distended. X-ray examination nevertheless indicated that the stomach was nearly empty. Stereoroentgenograms, however, showed that the small intestine and colon contained an enormous amount of material, although they also were far from completely filled. The sense of unusual fullness, therefore, was not due to a full stomach, but due to the considerable filling of the small intestine and colon. A similar filling is evidently one factor explaining the "poor appetite" commonly associated with constipation. The finding that my stomach was nearly empty when I felt extremely full incidentally explained a previous observation that I could enjoy a substantial meal of nutritious food after feeling stuffed to the hilt by ingested inert materials. This also suggests that the sense of more or less complete fullness following the ingestion of large amounts of non-nutritive materials comes from the intestines and not from the abdomen in general.

I began trying to dispel a desire to eat by ingesting inert materials in 1908 in an attempt to make it easier to practice fletcherism, the principles of nutrition promulgated by Horace Fletcher (3, 4). Fletcher's advice was to eat only in response to a normal appetite which he maintained was "indicated by a desire for *some particular* simple food accompanied by a 'watering of the mouth'." I had no such appetite at that time. Instead, I seemed to be eating in response to what Fletcher described as "false appetite" — "a general discontent of the body . . . often expressed by 'all gone-ness' or stomach craving and calls for *something*, ANYTHING! to smother the discomfort of present or recent indigestion" (3 — page 6). Fletcher's advice was to ignore "false appetite" and wait for the

return of a normal appetite, but I found it extremely difficult to ignore "false appetite" (at the age of 19). As a "false appetite" (according to Fletcher) did not indicate a need of food and merely called for something to dispel the discomfort due to "present or recent indigestion," it seemed to me that an inert, non-decomposable and non-nutritive material should serve the purpose. I first tried using charcoal because this was recommended as a remedy for flatulence and it could not decompose in the digestive tract, but I could not swallow enough to dispel the desire to eat. Next, I tried sand. I had no difficulty swallowing moist sea sand seasoned with salt. The swallowing of about four ounces of sand made me feel as if I had eaten a meal. In fact, it made me feel for a time as if I had eaten too much. I did not expect an inert material to serve that well and I was therefore greatly impressed. The sand proved to be too heavy and too irritating for repeated or frequent use but it stimulated a search for a material that would serve the same purpose but that would be better adapted to the requirements of the digestive tract.

Shortly after I tried sand, I tried rounded glass beads as they did not seem likely to be irritating, but I used only small amounts in 1908 and was not satisfied that their use would be practical even if they served to dispel the desire to eat. However, for a special purpose test, I swallowed about twelve ounces of the rounded glass beads in 1915 and found that I was hungrier after I swallowed them than before. Presumably, they stimulated strong gastric contractions. They seemed to be rolling out of my stomach as fast as I could swallow them but, as explained elsewhere (5), I found that they passed more slowly through the entire digestive tract than cellulose or ordinary food residues.

I found nothing more suitable than sand until 1914 when I first succeeded in swallowing cotton fiber. I tried swallowing cotton from time to time after 1908 but did not succeed until 1914 when I first tried it soaked in maple syrup. After that, I used less and less flavoring until I acquired the knack of swallowing it without any flavoring. As indicated in a preceding report (6), I preferred using it flavored with fruit juice. Thus, I found that I could keep myself stuffed all day (in 1914) with two ounces of cut up or chopped up cotton fiber. The fiber and fruit juice usually satisfied me completely two or three days at a time. Then a desire (normal appetite?) for more nourishing food developed and this could only be satisfied by eating appropriate food during one or two days. After that, cotton and fruit juice usually satisfied me completely again during two or three more days. However, the cotton fiber matted too much in the digestive tract and the fiber and fruit juice produced anal pruritus (6). A more suitable non-nutritive material than cotton fiber was therefore needed.

A failure to find a natural fiber, pulp or pith that would serve better than cotton fiber led me to try making a more suitable form of cellulose artificially. Thus, in 1915, I succeeded in making a spongy or

agar-like form of alpha-cellulose by the viscose process which is used in making rayon and cellophane. The freshly prepared cellulose was as easy to eat as macaroni (after being flavored with fruit juice) and I thought that this form of cellulose would be ideal but it took me an entire week to make enough for one large meal. This led me to try interesting others in the idea but the difficulties that I met (between 1915 and 1917) need not be mentioned here.

I first learned of the use of non-nutritive materials in the starvation treatment of diabetes in 1917 when I served as a "guinea-pig" for a study of hunger by Dr. Carlson at the University of Chicago (7). As a result, I began corresponding with Dr. Frederick M. Allen, who originally demonstrated the value of the starvation treatment of diabetes at the Hospital of the Rockefeller Institute of Medical Research. I found that Dr. Allen already had been trying to get manufacturers of diabetic specialties to provide a flour made out of cotton, but the manufacturers found no practical way to grind cotton. I succeeded in pulverizing cotton in 1918 but found on personal trial that it took much more of the pulverized cotton than of the fibrous cotton to produce a sense of fullness. In fact, I thought that pulverized cotton would be practically worthless for this purpose, but Dr. Allen assured me that a powder would be of value because talcum powder already had been used and its use was merely objected to on general principles. Hence, I put a cellulose flour (Cellu Flour) on the market in 1919, but I also tried to encourage the use of a fibrous edible cellulose (somewhat more fibrous than the Cellu Flour B which is now obtainable) because it took less to produce a sense of fullness. However, the cellulose flour was used in the diabetic diet generally mixed with washed bran and other materials and the non-fibrous flour was preferred because it could be mixed more easily with other things. In my opinion, one consequence of the use of various other materials with cellulose flour was that the value of using mainly relatively pure cellulose in the diet was not observed or appreciated by others. In any event, I was interested mainly in the use of pure cellulose in the general diet and I therefore disposed of my manufacturing interests in cellulose flour in 1923 when insulin became available and it was also thought that non-nutritive materials would no longer be needed in the diet of diabetics.

IS THERE A NORMAL BULK-HUNGER?

As already indicated, I first believed that inert materials merely dispelled the desire to eat which Fletcher called "false appetite." Fletcher did not distinguish between appetite and hunger and his basic ideas concerning hunger were apparently derived from the teachings of Dr. Edward Hooker Dewey, advocate of the no-breakfast plan and fasting cure (8). Dewey and other advocates of the fasting cure (9) regarded the desire to eat, particularly in conditions of disease, to be mainly "habit hunger," "unnatural hunger" or "abnormal hunger." Fasting was believed to restore health and normal, natural or instinctive hunger.

Fletcher simply presented the central idea in the fasting cure in more acceptable form by advising one to ignore "false appetite" and wait for a normal appetite to develop. Fletcher moreover supported his explanation of a normal appetite or normal hunger by Pavlov's (then recent) findings concerning the appetite gastric secretion (10).

The discovery of the X-rays and the manufacture of more suitable balloons and tubes for studying the work of the digestive tract seems to have focused scientific attention more on the mechanics of the digestive tract and this, in my opinion, led Hertz (Hurst) in England and Cannon, Carlson and Alvarez in the United States to over-emphasize the importance of mechanical factors in hunger and other sensations related more or less to the work of the digestive tract. I did not learn of the explanation of hunger advanced by Carlson and Cannon until Carlson's monograph on hunger (11) came to my attention in 1916. My immediate impression was that the desire to eat which Carlson and Cannon regarded as hunger was the desire to eat that Fletcher regarded as "false appetite." As a result, I served as a "guinea-pig" for a study of hunger by Dr. Carlson in 1917 (7). After ten weeks during which the motor activity of my stomach was recorded practically every day, I was not convinced that the desire to eat associated with the gastric "hunger" contractions represented normal hunger. It seemed to me that to regard the sensations due to the periodic gastric "hunger" contractions as normal hunger was to justify the eating of highly nutritious food at times when little or nothing but non-nutritive substances should be ingested.

After I disposed of my manufacturing interests in cellulose flour, I gave my own desire to eat close attention again and found, in 1924, that the gastric "hunger" contractions were felt without any desire to eat whatever when the stomach became empty after eating a large amount of easily digested and rapidly absorbed food (12). The desire to eat therefore appeared to be basically related to the need of food and only indirectly to the periodic gastric "hunger" contractions. The application of this finding since 1924 enabled me to avoid overeating without depending on the use of non-nutritive materials, but this may be partly explainable by the fact that I also had become older and "stomach craving" was not as imperative as earlier. Besides this, I continued to use some non-nutritive materials but mainly for laxative purposes or general intestinal comfort.

Further explanations of hunger and/or appetite were found later (13), but observations made on rats in recent years suggest that there may also be a normal bulk-hunger or "hollow hunger" that leads to the overeating of food when it is not satisfied by the ingestion of enough inert materials. That is, in 1929, McCay (14) reported the use of ground cellophane as a source of roughage in the diet of rats. This naturally interested me as I made the spongy cellulose in 1915 by the process used in making cellophane. A personal trial of ground No. 300 glycerine-free cellophane, however, indicated that it was too

irritating for liberal use even when ground relatively fine. Tests on rats also showed that it produced scratch marks in the colon. Nevertheless, McCay and his associates (15) found that rats fed a diet including ten per cent ground cellophane lived longer than rats on their stock diet and longer than rats raised by Campbell (16) on the superior Sherman and Campbell diet (17). The cellophane-fed rats were retarded in growth and McCay (18) believed that a retardation of growth prolongs life. McCay and his associates (15) therefore attributed the longer life span of the cellophane-fed rats to the retardation of growth and not to the cellulose. My personal experience with cellulosic materials naturally inclined me to believe that the practically pure cellulose helped to prolong the life span and that the retardation of growth was largely incidental and due to the irritating texture of the ground cellophane. In short, I believed that the life span of rats could be prolonged without a retardation in growth by using a more suitable non-nutritive material than ground No. 300 cellophane in the diet and an opportunity to test this idea developed in connection with a study of the effect of intermittent fasting and other factors on the life span of rats (19, 20). The detailed results will be reported in a separate paper (21) but, as already suggested, the results indicate that rats, like humans, tend to eat too much rich food unless the diet contains a substantial amount of non-nutritive material.

A simple explanation of the tendency to overeat is that the normal desire to eat, like the normal sex interest, is greater than the need for the survival of man under civilized conditions or of the rat under laboratory conditions. One object of eating is to dispel the sense of emptiness and central and secretory factors tend to impel a continuation of eating until a sense of more or less fullness develops. When rich food is used to satisfy the desire to eat, the volume of food needed to produce a sense of moderate fullness is likely to be more than enough for normal growth and maintenance.

In spite of occasional food shortages, overeating or too much catering to the appetite (taste) is, in my opinion, the number one problem of civilization (22). I do not believe that this problem can be solved by urging people to use more bulky natural foods. The trend has been away from the use of such foods because they are generally distasteful, irritating or highly fermentable. Fletcher advised the rejection of all food that did not melt in the mouth because it was likely to decompose in the digestive tract and increase "false appetite." On the other hand, Dr. Kellogg of Battle Creek, who otherwise promoted fletcherism, believed that large amounts of roughage should be ingested to reduce or prevent autointoxication. My idea was to resolve this dilemma by using materials that resisted decomposition in the digestive tract. I also thought that such materials would serve to reduce the intestinal flora without necessarily changing it, as proposed by Metchnikoff. My experience with the use of cotton fiber at first suggested that some form of alpha-cellulose would be ideal, but I am not

so sure about that now. In 1921, I brought my cellulose flour to the attention of Prof. Carl von Noorden and he pointed out that one of his pupils (23) had already published a paper in 1902 concerning the value of using a bread including purified cellulose in the treatment of constipation, obesity and diabetes. Apparently the bread or the included cellulose was not satisfactory as its use was unknown to American diabetic specialists in 1921, but von Noorden's school was evidently the first to recognize the value of purified cellulose in the diet. About five years after I put cellulose flour on the market, the H. J. Heinz Company put prepared foods on the market, including rice hull cellulose (24, 25). The amount included in the prepared foods was only claimed to give the products a "vegetable (roughage) effect." Unfortunately, the publication of a report by Morgan (26) based on the results of using the irritating ground No. 300 cellophane seems to have halted the promotion and commercial development of purified cellulose for use in the human diet. The situation became further complicated by the view of Williams and Olmsted (27) that the laxative effect of cellulose materials is due to breakdown products which are best provided by hemicellulose. Highly laxative bulk-formers do not serve well as dispellers of "hollow hunger" as they tend to promote emptiness. As a smooth and only moderately laxative bulk-former the best I found was a combination of ground purified kapoc and psyllium seed husks (28), but the second World War cut off the supply of suitable kapoc. However, more satisfactory products than any now obtainable will

undoubtedly be provided when a sufficient demand develops.

Finally, the question concerning the possible misuse of otherwise satisfactory non-nutritive materials should perhaps be considered. There can be no doubt that excessive amounts of non-nutritive materials can be ingested just as too much rich food may be eaten. One result is that the amount of bulk needed to produce the same filling effect is likely to be increased. There is no doubt that I used too much cotton fiber between 1914 and 1917 when I often stuffed myself with cotton at times when nutritious food would have served better. Consequently four ounces of cotton were needed daily in 1917 to have an effect similar to two ounces in 1914. However, the amount of bulk needed was again reduced after a year of military service (1918-1919) during which little extra bulk was ingested. The use of all bulky materials may, of course, be contraindicated in some cases. Concerning the other extreme, my experience suggests that no normal individual is likely to starve to death as a result of keeping stuffed with non-nutritive materials as an irresistible desire to eat — real hunger — is likely to develop sooner or later.

SUMMARY

Evidence is presented indicating that, although non-nutritive materials dispel the desire to eat only transiently by filling the stomach, they tend to dispel the desire to eat more thoroughly by filling the intestines. It is believed that relatively pure cellulosic bulk-formers which resist breakdown in the digestive tract serve the purpose best.

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Book Reviews

Peptic Ulcer: Its Diagnosis and Treatment. By I. W. Held and A. A. Goldbloom, pp. 382, Springfield, Ill., C. C. Thomas, 1946.

This book is written from the internist's point of view and interests. It stresses the diagnostic and therapeutic aspects in a manner designed to appeal to the general practitioner, military doctor and medical student who is either too busy or not sufficiently grounded to attempt a more thorough analysis. The title implies a great ambition which is not quite realized by the authors. However, for the purposes intended the book would appear to be perfectly adequate. The authors maintain a conservative attitude in their views on therapy, a point to be highly commended in times when hormones, vitamins, protein hydrolysates, psychotherapy, roentgen rays, and many other agents and procedures have been prescribed without either an adequate rational or experimental trial.

Food in Health and Disease. By Katherine Mitchell, B. A. and Genevieve Gormican North, B.A., pp. 616, (\$3.50), F. A. Davis Company, Philadelphia, Pa.

This is the fourth edition of a well-known and decidedly practical treatise on dietetics. As the authors emphasize, the starvation conditions now present in many parts of the world have rendered the general subject of nutrition extremely topical. Mrs. North,

whose work at Michael Reese Hospital is outstanding, has brought a somewhat fresh point of view to the whole text, whose fundamental characteristics, nevertheless, remain unchanged. While the book is designed primarily for nurses, the simplification of the data will not be resented by many of us M.D.'s.

"A. D. A. Forecast," published by the American Diabetes Association, for the general public. A sample copy of this, as yet unpublished, monthly magazine, has been received. The magazine is for the laity, and is meant to give the physician additional aid in the treatment of his diabetic patient. Each month the diabetic may thus receive a message of importance written by authorities in the field. Basic facts on diets — also inspirational material as well! The Association desires patients to subscribe through their doctors. Subscription blanks may be obtained from the American Diabetes Association, Inc., 1 Nevins Street, Brooklyn 17, New York. The rate is only \$2.00 per year. The copy received contains articles by Elliott P. Joslin, Yale S. Nathanson, Herman O. Mosenthal, Joseph A. Barach and Sister Maude Behrman. The Editor is Elizabeth M. Mullann. The first regular issue will be in January, 1948. The publication of this journal represents the Association's first step in an educational program for the laity. Congratulations, A. D. A.!

Abstracts Of Current Literature

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CLINICAL MEDICINE

Stomach

FELDMAN, M.: *Mucosal deformities of the greater curvature of the stomach.* (Radiology, August 1947, Vol. 49, No. 2, 152-161).

The purpose of this paper is to point out and emphasize the fact that the greatest caution must be taken in the interpretation of mucosal abnormalities and filling defects of the greater curvature of the stomach. This is especially important in the cases presenting defects that do not conform to the usual disease pattern. Repeated roentgen studies are essential in all doubtful cases and confirmatory information obtained by thorough clinical investigation and gastroscopic studies is necessary. An unequivocal diagnosis cannot always be made solely on the basis of the gastric roentgen findings. A study of the subsequent clinical developments over a period of months is essential

and often necessary to establish the significance of non-conforming disease patterns presenting deformities of the greater curvature.

A group of unusually interesting cases is presented to illustrate some of the difficulties encountered in the roentgen diagnosis of non-conforming disease patterns of the mucosa of the stomach. The filling defects shown in the roentgenograms were strongly suggestive of a primary gastric lesion. The presence of marked hypertrophy of the gastric mucosal folds is not ordinarily consistent with carcinoma. In carcinoma the folds are usually obliterated. However, these changes could fit into the picture of Hodgkin's or lympho-blastomatous disease and syphilis. Great enlargement of the mucosal folds due to hypertrophy is consistent with benign giant gastric mucosa. Extensive gastric deformity of the greater curvature with unusually marked serrations may be due to a gastritis associated with peptic ulceration.

FAIRCHILD, G. C. AND SHOEFER, A.: *Irradiation of gastric cancer.* (Brit. Med. J., Aug. 16, 1947, 243-247).

The authors describe a developed technique for the application of radiation therapy directly to carcinoma of the stomach through a wide incision and exposure. Although the end results were not too happy even in the cases in which the lesion appeared limited to an area that could be irradiated, it is probably true that much could eventually be accomplished by working out suitable techniques for this procedure.

Bowel

DURAN-JORRY, F.: *Histopathology of the semi-squamous epithelial layer in the colon.* (Rev. Gastroenterology, Sept. 1947, Vol. 14, No. 9, 595-602).

This first-prize essay in the National Gastroenterological Association's 1947 Prize Award Contest, consists of a well-illustrated study of the semi-squamous epithelial layer which covers the whole of the colon and rectum, commencing in the small intestine and continuing throughout these organs to join the "stratum corneum" of the anal skin. Containing an important net-work of capillaries, it does not stain with mucin stains. Its thickness provides the colon a strong protection against the acid contents of the organ.

KING, W. E. AND FRENCH, E. L.: *An outbreak of dysentery caused by shigella schmitzi.* (Med. Jour. Australia, August 2, 1947, Vol. 11, No. 5, 136-138).

Although sporadic infections due to *Shigella Schmitzi* have occurred in all the larger epidemics of bacillary dysentery during the war years, this is the first reported outbreak in which this organism was the sole etiological factor. About 47 per cent of the 51 cases were definitely toxic. A small group were hospitalized because of pyrexia of undetermined origin. Finally there was a third group in which the symptoms were very mild and diarrhea not an obstructive symptom. In all cases diagnosis was made by stool culture. Sulfaguanidine was the treatment used. No mention is made of any deaths from the disease. The epidemic was controlled through sanitary measures and isolation of cases.

BASTRUP-MADSEN, P.: *Plasmacytoma of the intestine.* (Nordisk Med., September 19, 1947, 1919-1920).

Plasma cell tumours may occur outside the bone marrow, in such case commonly originating in the air passages. Only eight cases of plasma cell tumours in the intestinal tract have been previously described in the literature. A case is reviewed here of a malignant plasma cell tumour originating in jejunum. The patient, a 49 years old man, had been ill for three months with vomiting. X-ray examination showed a tumour in jejunum 50 cm. from duodenum. The tumour was completely removed in healthy tissue

by operation. The lymph nodes had apparently not been invaded. Microscopical examination showed that the tumour consisted of plasma cells. After two months a tumour appeared at umbilicus. It consisted of plasma cells and was considered to be of metastatic origin. This tumour was removed but a fistula remained which in spite of x-ray treatment never healed. The patient grew weaker and weaker and died a year after the first symptoms had set in. Necropsy revealed great metastases at the mesenteric lymph node; peritonium and the omentum were overgrown with tumour masses. The bone marrow was not infiltrated and there was no reproduction of the jejunal tumour.

The sedimentation rate had all the time been 10 mm. (1 hour). Attention is directed to the fact that, whereas the sedimentation rate always is very high in myelomas, it is normal or only slightly raised in extramedullary plasma cell tumours and it is not raised until there is metastases of the tumour to the bone marrow. Further investigation in connection with these problems is called for.

BROWN, PHILIP W.: *Inflammatory diseases of bowel.* (Proc. Staff Meet. Mayo Clinic, v. 22, p. 155, 1947).

The author has divided inflammatory diseases of the bowel into specific and non-specific groups. The most commonly encountered in the specific group are due to organisms of the Genera *Salmonella*, *Shigella* and *Staphylococcus* and the parasite *E. Histolytica*. Sulfadiazine, he believes, is the drug of choice for treatment of bacillary dysentery and the institution of two courses of emetine hydrochloride with two to three courses of carbarone for the treatment of Amebiasis.

In the non-specific diseases chronic ulcerative colitis and regional enteritis are most commonly observed. The author feels that there is no drug, antibiotic agent or surgical procedure for these conditions that are more than of assistive value. He believes there are three factors that often precipitate the disease or cause a relapse: (1) emotional and mental stress, (2) intolerance to one or more ordinarily excellent food items, and (3) acute recurrent infections such as the common diseases of the upper respiratory tract or acute diarrhea.

SEWARD, C.: *The diagnosis and treatment of spastic colon.* (Med. Press, v. 127, p. 289, 1947).

Colon disorders give rise either to visceral or somatic pains. The visceral pain is probably due to increased muscular tension produced by either spasm or stretch. Somatic pain is probably the result of either peritoneal inflammation or traction.

Spastic colon is predominantly a disease of the female. It occurs in middle age. Allergy has been found to be the commonest external cause. Of internal causes arising in the digestive tract, reflex colonic spasm and constipation are most frequently found in association with peptic ulcer, chronic and acute cholecystitis, chronic appendicular disease, diverticulitis, and

dysentery. Renal calculi may produce reflex spasm of either colon or ileum, as may also salpingitis. Plumbism, of course, is known to cause painters' colic and should be borne in mind. Psychogenic colonic spasms may be considered but the services of a psychiatrist are usually necessary to discover these. Careful tests and examination are necessary to establish the right diagnosis.

In colonic spasm the pain may be distributed to a more or less localized area or be diffuse. The pain may vary from a dull ache to an acute colic. The pain may be continuous or intermittent.

Constipation is usual, though diarrhea may also occur. Epigastric discomfort due to reflex pylorospasm may be present and vomiting may occur. Symptoms and signs similar to those in gastric distension from aerophagy may be presented.

Treatment depends entirely on etiology and is largely symptomatic. Psychotherapy, avoidance of roughage, diet, special enemas or aperients, belladonna, and phenobarbital are recommended.

WAKEFIELD, E. G.: *Medical aspects of malignant lesions of the anus, rectum and colon.* (Proc. Staff Meet. Mayo Clinic, v. 22; p. 153, (April 16) 1947).

Diagnosis of a malignant lesion should not be included in the patient's record without a pathologic report of confirmation. In the age group in which malignant lesions of the colon, rectum and anus are most likely to occur there are usually coexisting diseases which make the progress of the surgeon hazardous. These include infection of the respiratory system, cardiovascular and renal disease, gastrointestinal disorders not connected with the malignancy, diabetes, hyperthyroidism, etc. These diseases are mainly chronic and tend to relapse or recur after operation.

Generally no preoperative treatment of these other systems is necessary unless there is actual decreased functional activity. If the organs show decreased function their activities should be supported by appropriate measures (insulin, digitalis, antibiotics, etc.).

In most cases metastases from the rectum and colon occur in the liver. However, an enlarged liver in the patient with a lower bowel tumor does not always mean metastatic advancement.

Anemia due to loss of blood from chronic bleedings must be attended to, preferably by blood transfusions.

Saline laxative is given preoperatively to produce a liquid stool and colonic irrigation is used too. If operation is postponed it should be remembered that the patient is receiving laxatives and enemas. Also the preoperative diet, high in carbohydrates, is not adequate and should not be prolonged.

BASTENIE, P. A.: *Paralytic ileus in severe hypothyroidism.* (Lancet, v. 250, p. 413, 1946).

The author describes 29 cases having severe hypothyroidism and gastrointestinal dysfunctions. Constipation, megacolon and intestinal obstruction with distension were found present. It is suggested that in-

testinal paresis may be the earliest sign of importance indicating hypothyroidism.

WATT, J. AND GUTELIUS, M.: *Acute diarrhea in children.* (New Orleans Med. Surg. J., v. 99, p. 266, 1946).

The Shigella and Salmonella pathogens are responsible for most of the severe diarrheas in children. Probably 75 per cent of the acute diarrheas are due to these two organisms, with the Shigella group predominant. Since the Shigella bacillus but not the Salmonella bacillus can be affected by the sulfonamides, it is desirable to have identification in stool specimens made whenever possible. Agglutination results are difficult to interpret while complement fixation tests still remain to be developed.

Treatment is aimed mainly at restoring fluids and electrolyte balance. From 75 to 150 cc. of fluid per pound body weight are required per day at beginning. The continuous intravenous drip is preferred but single intravenous injections every four hours may be tried when the drip method cannot be used. Fluids by mouth may be given slowly if vomiting is not severe. Solutions of sodium bicarbonate or sodium lactate with Ringer's and dextrose solutions of the proper concentrations are used. The daily intake of fluid to maintain hydration once electrolyte balance is again normal is about 60 cc. per pound per day. Ketosis may be avoided by giving dextrose. Whole blood, concentrated plasma, and amino acid solutions are valuable, particularly when the patient's serum protein level is low.

Sulfadiazine, sulfapyrazine, and sulfathiazole are valuable in combatting Shigella infections. Dosage should be adjusted to the response, as judged by the effect on the organisms in stool cultures. The urine must, of course, be maintained alkaline to prevent renal damage.

A high protein diet is indicated. Medications such as apple pectin, kaolin and agar may be helpful. Sedation may be employed in cases with pain or marked vomiting.

RUBENSTEIN, A. D. AND FOLEY, G. E.: *Epidemic of diarrhea of the newborn in Massachusetts.* (New England J. Med., v. 236, p. 87, (Jan.) 1947).

There have been 19 outbreaks of epidemic diarrhea reported among the newborn of Massachusetts in the decade of 1935-1945. The mortality rate was 33.6 per cent, being 53 and 25 per cent among the premature and full term infants respectively. The morbidity was likewise greater among the premature. Nursing care and procedures involved in preparation of feeding formulas were frequently poor. Bacteria were shown among many of the materials to which the infant was exposed, such as thermometers, hands, nursing bottles, etc. Overcrowding was usual. Sterility of individual bottles must be insured, overcrowding prevented and other sanitary measures made essential standard procedures to prevent spread of the infection

Pancreas

PUEBOW, C. B., LOONEY, W. E. AND RISLEY, T. S.: *Acute pancreatitis*. (Am. J. Surg., v. 72; p. 818, (Dec.) 1945).

Diagnoses were established at operation or autopsy. Of the 17 autopsied cases, 65 per cent had acute hemorrhagic pancreatitis, the remainder acute suppurative pancreatitis. About half of the cases also had gall bladder disease.

Acute hemorrhagic pancreatitis gave similar, but rather more severe, symptoms to acute edematous pancreatitis. Serum amylase determinations were extremely helpful in diagnosis and in selecting the time for surgery. The acute pancreatitis must be differentiated from perforated peptic ulcer since the latter is a case for emergency surgery while the former should not be operated on. The nature of treatment is conservative. Measures taken include all those which give the patient and his digestive tract complete rest and which support the vascular system and provide electrolyte and fluid balance. Surgery should be considered only after the acute phase has subsided.

Liver and Gall Bladder

HERSTMANN, D. M., HAYENS, W. P. AND DEUTSCH, J.: *Infectious hepatitis in childhood: a report of two institutional outbreaks*. (J. Pediat., v. 30; p. 331, 1947).

Catarrhal jaundice in children and infectious hepatitis in adults are probably identical diseases. It is milder in children and of shorter duration.

In outbreaks in two institutions housing children and adults only the adults became ill enough to require hospitalization. Onset of the prodromic phase could be dated from appearance of headache, fever, abdominal cramps, and vomiting and nausea, while the icteric phase dated from the appearance of jaundice. In the icteric phase the child feels much better than in the prodromic phase. Complications were rare. The prodromic phase lasted five days or less, the icteric phase ten days. Fever was noted usually only in the prodromic phase and was absent by the time jaundice had appeared.

Ulcer

MARGARETTEN, E. AND KAMER, F. A.: *Peptic ulcer treatment with protein hydrolysate*. (New Jersey Med. Soc. J., v. 49; p. 219, (June) 1947).

Three ulcer patients who did not show improvement on the Sippy regime did show good improvement when placed on protein hydrolysates. However, only one patient showed healing radiologically; in the other two the ulcers still remained. The improved feeding and general benefits were mainly symptomatic. The daily dosage level of protein digest was maintained at 44 grams per kilogram body weight given in pineapple juice with dextrinmaltose and sugar added. The

authors attribute the results to the acid binding properties of protein and believe that protein digest is a modification of choice in peptic ulcer.

HILSCHFELD, J. W., ALDOTT, W. E. AND SMATHERS, H.: *Use of chemotherapy as a possible means of reducing mortality rate in perforated ulcer*. (Am. J. Surg., v. 17; p. 54, (July) 1947).

Between 15 and 20 per cent of the patients subjected to surgery for acute perforation of a peptic ulcer die shortly after operation. More than three quarters of these operative deaths are due to peritoneal or pulmonary infections. The bacterial agents involved are usually susceptible to either penicillin or streptomycin. The authors advocate chemotherapy to lower the operative death rate. That chemotherapy is only a means to combat infection and is not a substitute for good surgical intervention is stressed. Both preoperative and postoperative care must also be good.

SURGERY

NETELIN, H. A. AND WALTERS, W.: *Obstruction of vitallium tube by biliary sediment*. (Proc. Staff Meet. Mayo Clinic, v. 22; p. 424, (Sept. 17) 1947).

Few papers have stressed the ever-present danger that the vitallium tube used in biliary duct anastomoses may become obstructed. At the Mayo Clinic the vitallium tube has been used in 74 cases. Eight tubes had to be removed because of obstruction and a ninth tube was found obstructed at autopsy. The obstructing material is usually composed of cholesterol and bilirubin, together with insoluble calcium, pigments and organic debris.

Since any or all vitallium tubes may eventually become obstructed, the authors do not favor its use in bile duct surgery. The ideal procedure would be to use some sort of tube as a temporary splint, preferably one made of material sufficiently flexible to be either withdrawn after removal of stay sutures or one which will pass from the duct spontaneously.

POTT, E. J.: *Sulfazuridine and sulfathiazole in surgery of the colon*. (South Med. J., v. 49; p. 369, May, 1947).

Five years' experience with suodimylsulfathiazole (sulfazuridine) and phthalylsulfathiazole (sulfathiazole) in surgery of the colon are reviewed. When administered at the right time in the optimum doses these drugs were found to change the flora of the bowel contents in favor of those of lesser pathogenicity. Operative procedures could be carried on on the colon with greater safety. Earlier healing was favored and the incidence of postoperative infection was reduced. The author emphasizes that the antibiotics do not replace good surgical methods; their value is greatest only as aids in preparing the operative field for application of these methods.

ODLERSBERG, D. AND HAMMERSCHLOG, E.: *The postgastrectomy syndrome*. (Surgery, v. 21; p. 720, 1947).

Unpleasant sensations of fullness, nausea, belching and dizziness may arise during or following a meal in the patient who has had a partial gastrectomy for peptic ulcer. These are primarily due to the abnormal motor physiology of the stomach and intestine resulting from the unnatural anastomosis. Dizziness, sweating, headache, fatigue and other symptoms of hypoglycemia are the result of rapid post-prandial rise in blood sugar with a rapid fall to lower than normal levels.

A recumbent position is helpful, both early and late effects of a meal being greatly reduced. B. M. R. was found low in 13 patients with subtotal gastrectomy but the blood proteins and blood picture (except for hypochromic microcytic anemia) were normal. Rapid emptying of the gastric pouch with rapid distension of the jejunum by overfilling were present. Hypoglycemia was not present during fasting but only in rebound about two hours after a test meal. This was due to oversecretion of insulin. Occasionally fatty acids, soaps, and muscle fibers were found in the stool but the stools were not characteristic of sprue.

WRIGHT, L. T., PRIGOT, A. AND HILL, JR., L. M.: *Traumatic rupture of the liver without penetrating wounds*. (Arch. Surg., v. 54; p. 613, 1947).

Traumatic rupture of the liver without penetrating wounds is reported in 32 cases. Apparently this condition occurs more commonly than one would suspect from the literature. A diagnostic procedure of great value is the abdominal tap. Symptoms may be masked by associated lesions. Hemorrhage control is of paramount importance and surgery must be used. The use of hemostatic agents such as fibrin foam and oxidizable cellulose gauze are recommended.

Early diagnosis and operation, counteraction of the shock, control of hemorrhage, and prevention of infection by means of antibiotics, together with careful postoperative nursing care can successfully reduce the mortality rate.

EXPERIMENTAL MEDICINE

Secretion

ZIPKIN, I.: *Citric acid in saliva*. (Science, v. 106; p. 343, (Oct. 10) 1947).

Citric acid was found in saliva of adult men in greater concentrations than hitherto suspected. The content was 0.5 to 2.0 milligrams per cent citric acid, with the higher values being obtained at 1 p. m.

The relation of salivary citric acid to dental erosions and dental caries suggests further studies: Dental tissue is decalcified by the citrate ion and citrates in practically neutral drinking fluid have a pronounced destructive action on dental tissues.

MONTGOMERY, M. L., ENTENMAN, C. AND CHAIKOFF, I.: *Pancreatic juice is a rich source of the anti-fatty-liver factor*. (Am. J. Physiol., v. 148, p. 239, (Jan.) 1947).

Depancreatized dogs kept on insulin ultimately develop fatty livers. It has been known for some time that feeding of raw pancreas prevents this. Dog's pancreatic juice, when fed daily to the depancreatized dog in amounts as little as 10 cc. has a similar effect. The livers of dogs receiving pancreatic juice can be kept normal for as long as five months. The plasma choline concentration of these dogs was raised. Probably the anti-fatty-liver factors in raw pancreas and in pancreatic juice are identical.

Motility

ANNEGERS, J. H. AND IVY, A. C.: *The effect of dietary fat upon gastric evacuation in normal subjects*. (Am. J. Physiol., v. 150; p. 461, (Sept.) 1947).

It has previously been shown that olive oil delays gastric emptying of an Ewald or gruel meal in man. In this study, thirty subjects were given 1500-caloric meals after fasting six hours. The meals contained 53, 77, and 120 grams total fat of which 25, 50 and 80 grams respectively were added lard or Crisco. Four hours after each test meal, each subject was given 100 cc. of 20 per cent barium sulfate suspension and upright A-P x-ray films were made. All data were treated statistically by the method of analysis of variance. Twenty-five subjects showed a delay at four hours when the fat content by net weight was increased from six to eight per cent, and 27 subjects showed delayed gastric evacuation when the fat was increased from eight to fourteen per cent. No significant differences were found between lard and the hydrogenated vegetable oil in their effect upon gastric emptying. No gastrointestinal symptoms followed many of these test meals. The gastric inhibition occurring with increased fat content was consistent for given individuals.

FENTON, P. F. AND PIERCE, H. B.: *Response of the gastrointestinal tract to ingested cereal starch*. (Am. J. Physiol., v. 148; p. 296, (Feb.) 1947).

Young mature rats fasted 48 hours were fed highly refined cooked cereal in accurately weighed amounts. The contents of the stomach and intestine were then analyzed at the end of the absorptive period for starch, sugar, etc. The larger the meal the higher was the emptying rate. Regardless of the amount fed, the fraction emptied in any given time interval was nearly the same. Presumably the increase in the size of the meal stimulated the emptying mechanism, perhaps by raising intragastric pressure. The absorption rate also increased with the size of the meal and decreased with time. The cereal was evacuated by the stomach and absorbed in the intestine in the same manner as dextrose fed at similar levels.

Pathological Chemistry

BRIEGER, H. AND FRIEDMAN, M. H. F.: *Thymol-barbital turbidity test in experimental carbon tetrachloride poisoning*. (Occupational Med., v. 2; p. 463. (Nov.) 1946).

In 93.3 per cent of a series of rabbits receiving oral carbon tetrachloride the serum or plasma thymol-barbital turbidity reactions were above those found in a series of untreated rabbits. Both plasma and serum gave equally reliable results. Neither aging of the serum or plasma affected the reaction: in this respect it differed from the known effects of aging on the cephalin-cholesterol flocculation test.

Following development of liver injury by carbon tetrachloride the rabbits developed lipemia and also reduced their food intake. Neither the lipemic state of the blood or the fasting condition of the animal were found to be responsible for the positive thymol-barbital turbidities. Starvation in untreated animals tended to produce lower turbidity indices than in fed untreated rabbits but all values fell within the same range. The lipemia of carbon tetrachloride poisoning as well as that of dietary origin is abolished by heparin.

ARCHIBALD, R. M.: *Determination of lipase activity*. (J. Biol. Chem., v. 165; p. 443, 1946).

Determination of lipase activity is made at the end of one hour's reaction time. The substrate is an aqueous solution of a derivative of sorbitan monolaurate. The fatty acids formed by lipolytic action are titrated in the usual manner. The advantages of this procedure lie in the complete solubility of the substrate in water.

WACHSTEIN, M. AND ZAK, F. G.: *Distribution of alkaline phosphatase in the human liver; a study of post-mortem material*. (Arch. Path. v. 42; p. 501, 1946).

The alkaline phosphatase of the bile capillaries shows greater than normal range of activity in obstructive jaundice. In cases dying with acute hepatitis or toxic cirrhosis the increased alkaline phosphatase was shown by the proliferating connective tissue. Necrotic livers were without increased phosphatase activity. The phosphatase is increased in all such conditions of liver damage which make excretion of the enzyme by the liver cells difficult.

METABOLISM AND NUTRITION

AUGUR, V., ROLEMAN, H. W. AND DEUEL, JR., H. J.: *The effect of crude lecithin on the coefficient of digestibility and rate of absorption of fat*. (J. Nutrit., v. 33; p. 177, 1947).

Large doses of cottonseed oil or of hydrogenated cottonseed oil caused diarrhea in rats. Addition of crude lecithin to the diet reduced the diarrhea. Lecithin also increased the rate of absorption of these fats. The various hydrogenated cottonseed oils were

digested to a greater degree when crude lecithin was present. The lipids were excreted as soaps rather than neutral fats or fatty acids.

CONN, J. W.: *The dietary management of spontaneous hypoglycemia*. (J. Am. Dietet. Assoc., v. 23; p. 108, 1947).

A brief review of carbohydrate metabolism in relation to blood sugar levels is given. Functional hyperinsulinism accounts for 70 per cent of the hypoglycemia cases. Symptoms begin only several hours after a meal; the fasting blood sugar levels are normal and attacks are not precipitated by fasting. Blood sugar tolerance curves (oral glucose method) show a sharp drop to below normal levels in two or two and one-half hours.

Glucose of the diet should be provided by protein, not carbohydrate. This prevents too rapid flooding of blood with readily absorbed glucose. The daily meals contain 120 to 140 grams protein and 50 to 75 carbohydrate.

Fasting hypoglycemia which is due to restricted carbohydrate intake is different from the hypoglycemia due to hyperinsulinism and may be found in Addison's disease, hepatitis, renal glycosuria and malnutrition of long standing.

ALEXANDER, B., LORENZEN, E., HOFFMANN, R. AND GARFINKEL, A.: *The effect of ingested mineral oil on plasma carotene and vitamin A*. (Proc. Soc. Exp. Biol. & Med., v. 65; p. 275, (June) 1947).

From the results of experiments on animals the Council on Foods and Nutrition of the American Medical Association concluded that mineral oil should not be used in foods indiscriminately but that its use should be under supervision of a physician. This was based on the reports of the harmful effects of mineral oil in interfering with the absorption of fat-soluble vitamins.

The study reported by Alexander et al. was performed on 25 subjects. Mineral oil as such, or in the form of a salad dressing, was taken over a long period of time, twice daily with meals. The diet was otherwise unrestricted. The vitamin A levels of the plasma were unchanged after several weeks but the carotene levels were moderately decreased. The authors concluded that the simultaneous use of mineral oil with food reduces substantially the amount of food carotene which can enter the body.

SHERMAN, W. C.: *Relative gastro-intestinal stability of carotene and vitamin A and protective effect of xanthophyll*. (Proc. Soc. Exp. Biol. & Med., v. 65; p. 207, (June) 1947).

Unsaturated fat acid esters destroy in the rat gastro-intestinal tract carotene which is fed simultaneously. This destruction of carotene is prevented by alpha-tocopherol.

In the present report the inclusion of Xanthophyll

in the diet protected from gastro-intestinal destruction the added free carotene, vitamin A alcohol and vitamin A acetate. Probably carotene and vitamin A are destroyed in the gastro-intestinal tract by enzymatic processes, possibly by the carotene oxidase which has been found in the mucosa of the rat stomach. The sparing action of Xanthophyll may be explained by the non-specificity of the enzyme, which favors destruction of Xanthophyll to the carotene or vitamin A compounds which are of similar molecular structure.

BLACK, D. A. K.: *Salt deficiency in sprue*. (Lancet, 251:671, (Nov.) 1946).

Ten patients with sprue, showing hypotension and asthenia, were studied. Serum sodium and chloride levels were low in all cases and the patients were in decided negative balance with respect to sodium and chloride. Sodium loss was mostly through the feces.

On a high salt diet the blood pressure rose, dehydration disappeared, the serum sodium and serum chloride levels were higher and diarrhea decreased. The authors suggest that the anorexia and the diarrhea, resulting in decreased intake and increased loss, were responsible for the low serum sodium and chloride values.

SCHUR, HEINRICH: *Die Isodynamie der Nahrungsmittel in ihrem zusammenhange mit den grundprinzipien des stoffwechsels und speziell den stofflichen bedürfnissen des organismus bei seinen leistungen*.

(*The isodynamy of nutrients in their relation to the principles of metabolism and the needs of the organism*). (Wien. Klin. Wochenschr., 1947, 59 No. 11, 12, 13).

The author summarizes the result of the research he has performed with various collaborators since 1897, especially with R. Burian, Kornfeld, Loew and Krcma. Starting from a number of special problems all their investigations were concerned with the fundamental question how the chemical processes can be brought into agreement with the energetic conception of life and the performances of the organs. The contradiction between chemical processes within the organs and the observations of the energy balance complicated the problems and aggravated its difficulties. The chemist's concept of a definite chemical process corresponding to a definite function did not tally satisfactorily with the opinion that any substance supplying energy could be used equivalently, and that the caloric value of nutrients is an accurate measure of their nutritional value.

Mechanisms utilizing directly a gradient of temperature for dynamic purposes do not exist in the organism. Therefore, the caloric evaluation of a nutrient by a purely thermodynamic device, analogous to our technical caloric engines, appeared quite infeasible. Moreover, all investigations showed that physiological performances required certain substances, the formation of which within the organism in turn implied

certain losses depending on the kind of the food. The isodynamic value, confirmed by observed facts and the independence of the total metabolism from the nature of the nutritional material, appeared incomprehensible. The insignificant differences found by various investigators were of no material help. In spite of the mechanism of thermic regulation, the observations of the author and his collaborators were incompatible with a cerebral or hormonal heat regulation. The possibility of a caloric reserve was absolutely insufficient to explain the great discord between facts and theory. Heat, should it account for the isodynamic effect of fat, carbohydrates, and other heat-supplying substances, had to be utilized in the process of muscular contraction itself.

The direct source of energy, as confirmed by most of the competent investigators, is represented by a glycogen-containing accumulator which supplies the needed energy through anoxidative dialysis. In order to repeat its action, this accumulator had to be rebuilt, for which process a supply of heat was indispensable. The assumption was suggested hereby that the required heat may be drawn from all chemical processes employed in the body.

Since glycogen, the principle source of heat, is resynthesized to the greatest part in the liver, it seemed no longer necessary to regard lactic acid as the only source of heat. Moreover, recent investigators have found that dextrose, needed for muscle action, is found in the liver and nowhere else.

Resynthesis represents a fermentative process, as does the splitting of glycogen, and could be assumed to take place on an endothermic basis. In restoring the consumed heat, all exothermic processes would suffice.

The R. G. T. rule of van t'Hoff is of great importance in the utilization of heat for muscular action. Heat supplied from outside the processes has a special significance for all fermentative processes. The rule's validity rests on the acceleration of molecular movements and does not depend on any temperature gradient. Thus the chain processes necessary for muscle action are easily realized after their release through exothermic processes. Anoxydative splitting provides the muscular energy. It originates from the energy used for the building up of the working substances which in last line is supplied by the various combustive materials. This explains the isodynamy of the nutrients in that supply. For the specific vital processes this substitution is not possible, because they are bound to definite substances, a part of which like the vitamins must be supplied from outside. Since the heat generated in the combustive processes is available for the body, the transformation of the nutrients does not necessarily imply a loss.

The far reaching general importance of the law of isodynamy derives from the fact, that life principally consists in work. Naturally the law is not valid for the material need and is limited by the waste, resulting from the distance in time and space between the processes of splitting and resynthesis.

The assumption, that all physiological actions rest

on the energy supply from chemical accumulators is at hand. Yet it is at present not satisfactorily substantiated because ample glycogen storages are not yet demonstrated outside of liver and muscles. But it serves well as a working hypothesis. The concept that the depots of fats and carbohydrates stand in the center of life and are not to be regarded merely as dead reserves was a great help in the authors' investigations of the insulin problem. — Heinrich Schur.

MCCORMICK, W. J.: *The changing incidence and mortality of disease in relation to changed trends in nutrition.* (Med. Record, Sept., 1947, v. 160; no. 9, 533-560).

Statistical data are presented to show the marked decline in mortality and case fatality of many infectious diseases within the past century.

The uniformity of this decline, in so many diseases and over such a lengthy period of time, suggests the operation of some major over-all factor improving natural resistance, compared with which our artificial control measures have played a minor or supplemental role. The existence of such a factor has been recognized by epidemiologists, but not yet identified.

The author advances the hypothesis that some major change in the trend of nutrition offers the most likely explanation, and singles out the greatly increased consumption of citrus and other fruits rich in vitamin-C as the unidentified factor. Correlated statistical data show a close parallel, in both time and extent, between the development of this nutritional trend and the mortality decline in infectious diseases.

The physiological action of vitamin-C is discussed in relation to its "anti-infecton" role, and the literature relative to the prophylactic and therapeutic use of this vitamin in infectious diseases is reviewed.

BRAESTRUP, A.: *Studies of the renal threshold for glucose, II.* (Nordisk Med., June 13, 1947, 1348-1349).

In 10 severe cases of diabetes mellitus the renal threshold for glucose (determined as reabsorbed glucose) was studied from the onset of glycosuria for two and one-half to three hours. The threshold proved to be fairly constant in the individual case, independent of the rise in blood sugar. During the first one-half hour of glycosuria, a small rise (26 to 30 mgm. per

cent) in the threshold was seen, followed by a decrease which lowered the threshold after three hours to a point below the original threshold.

MISCELLANEOUS

RAFSKY, HENRY A. AND HERZIG, WILLIAM: *Scleroderma with oesophageal symptoms.* (Gastroenterology, 6:1, 35, January, 1946).

It is well known today that scleroderma is recognized as the skin manifestation of a disease which affects several systems of the human organism. In the two reported cases, the skeletal, vascular and gastrointestinal systems showed typical alterations aside from the skin changes. The differential diagnosis may be confusing and misleading depending upon the signs and symptoms presented at the onset of the disease. The first case showed circulatory impairment in the hands and feet initially which could have been interpreted as Raynaud's or Buerger's disease. The dysphagia, which appeared later on, could lead one to suspect the patient had an idiopathic cardiospasm, a Plummer-Vinson symptom, neoplasm of the esophagus, a diverticulum or possibly a peptogenic disturbance. The patient finally presented almost simultaneously arthritic and skin changes which are frequently seen in osteo-rheumatoid arthritis.

The biopsy showed normal squamous cells. Perhaps the biopsy of the atrophic area did not penetrate deeply enough. The x-ray study of the esophagus showed that the lower half was markedly dilated with spasm (achalasia) at the cardia. Under the fluoroscope one could see the cardia relax after a while and the barium enter the stomach.

The findings were very similar in the second reported case. — Franz J. Lust.

LIPSCOMB, A. AND CRANDALL, L. A.: *Hepatic blood flow and glucose output in normal unanesthetized dogs.* (Am. J. Physiol., v. 148; p. 302, 1947).

Urea nitrogen determinations were made on the urine, portal vein blood and hepatic vein blood. The blood samples were obtained by the London technique of cannulating the hepatic and portal veins. On the bases of the urea nitrogens as indicators, the average flow of blood in the hepatic vein of the fasting dog was found to be 1.9 liters per kilogram body weight per hour. The hepatic output of glucose during the same period averaged 122 milligrams per kilogram.

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